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CHILDREN OF ALCOHOLIC FATHERS

By

INGVAR NYLANDER

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Translated by Basil and Dorothy Finer

To Sven Ahnsjö

WHO HOLDS THE FIRST SWEDISH CHAIR IN CHILD PSYCHIATRY

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PART ONE

Children of fathers under treatment at the City of Stockholm Temperance Board Clinic for Alcoholics, the Mariapoliklinik

The case histories of all subjects in Part I have been deposited in the Library of Karolinska Institutet, Stockholm

CHAPTER 1

INTRODUCTION

This investigation is primarily concerned with the study of childrens' mental adaptation in homes where the father is a chronic alcoholic. It developed from an examination of subjects whose fathers were receiving treatment at the City of Stockholm Temperance Board Clinic for Alcoholics in Wollmar Yxkullsgatan (the so called Mariapoliklinik), (Part I). Secondly, the investigation is intended to throw light on the clinical importance of alcoholism among fathers, in child psychiatric practice. For this purpose a supplementary analysis has been made over a five year period of inpatients at the Psychiatric Department of Kronprinsessan Lovisas Barnsjukhus (K.L.B.) in Stockholm (Part II).

Symptoms such as headache, nausea, palpitations, diffuse abdominal pain or tiredness, are often caused by a state of mental tension produced by emotional upsets in the home. Söderling (1952) has drawn attention to "two important and common factors underlying psychosomatic disorders in family and child: the insufficient mother and the alcoholic father", without describing any of his own cases.

In an investigation by the author (Nylander 1959), of patients seen by consultation from the medical and surgical wards of K.L.B., it was possible to show that among the children who came into the hospital with physical symptoms similar to those above, emotional upsets in the home such as mental illness, asociability or alcoholism in the parents, together with broken homes, occurred in a significantly higher frequency than among the children with other types of nervous symptoms, such as emotional instability, motor restlessness, anxiety and fear, etc. Among the cases showing pronounced, often hysterically-tinged physical symptoms, serious disturbances at home were almost always present.

Similar conditions were also reported by Ekström & Nylander (1959), who analysed a series of children after appendectomy. Among those cases where there was no positive finding at operation, there was a higher frequency of emotional upsets in the home, than among those where an acute appendicitis was found. The frequency of neurosis was about nine times higher in the former than in the latter.

Since the above investigations were carried out, special interest has been devoted to the mental symptom picture in the clinical work at the Psychiatric Department of K.L.B. In the cases where recurrent symptoms such as headache, palpitations, diffuse abdominal pain etc. appeared and where the physical examination gave negative results, the case history was studied with special care. It was then often

evident that serious disturbances existed in the home environment, even in cases where there had been no reason to suspect such disturbances from the beginning. This information was seldom given spontaneously by the parents. Only after repeated contact with them and the taking of some form of objective case history, could the true circumstances be revealed.

Because of these facts the following hypotheses were put forward: Children who live under stress, due to serious emotional disturbances in the home, may, as a result, react with non-organic physical symptoms. As a result, these children come up, either too late or perhaps not at all for psychiatric assessment and treatment. Instead they look for help from out-patient departments or hospitals for physical diseases, and in many cases, the true nature of the symptoms never comes to light.

To test these hypotheses scientifically the following questions were put:

1. Do children from homes which are seriously emotionally disturbed present nervous symptoms more often than children from homes where such disturbances can be assumed not to exist?

If such is the case

2. Are the nervous symptoms of these children of a special kind and

3. If so, can these nervous symptoms be correlated with any special factors in the environment?

4. How does the situation present itself for the children from homes which are seriously emotionally disturbed from the clinical point of view?

In order to answer these questions it was necessary to choose subjects who came from homes where emotional disturbances were most likely to exist. Furthermore the emotional stress needed to be relatively common, so that there would be sufficient subjects available, and should be of such character as to be easily defined and demarcated. Finally, it was also required that this emotional stress should have been prolonged.

It is inconceivable to make use of patients from child psychiatric out-patient departments or wards, since cases of this kind are most often specially selected. An overwhelming number of the children of parents who are co-operative, aware of the illness, or, for different reasons, forced to seek advice would, by this means, be included in the material.

The type of family from which it was considered suitable to select subjects, was that where one or both parents revealed psychopathological features of a certain degree of difficulty, where one or both parents showed pronounced difficulties in social adaptation, such as criminality, chronic disinclination to work, alcoholism, etc., or where problems of incompatibility existed between the parents, and where these led to divorce. In the cases where the mother is the immediate cause of the emotional disturbances, the children are often taken into care by the Children's Care Committee (Barnavårdsnämnden), and placed in a foster home or a children's home. For this reason, the above alternatives could be tested only in relation to the father.

In order to obtain children from homes where the father was mentally ill or revealed more serious psychopathological symptoms, it would have been necessary for him to have visited a doctor or been in

hospital or an institution. The more difficult cases among them could be expected to have been admitted for long-term treatment and care, and thus the home situation would not reveal a current emotional stress. Cases with such psychopathological symptoms that they caused emotional stress in the family, such as occur in aggressive and sadistic psychopaths etc., and whose family would have been suitable for investigation, could not be discovered. This was because it could be assumed that they lacked an understanding of the illness and so did not come to the doctor or hospital.

Neither were homes, where the father was asocial, considered suitable for investigation, since asociability, itself, cannot be said to be a criterion of an emotionally disturbed home.

Children of divorcees often live in an environment of emotional stress. However, they are often exposed to both positive and negative influences. There was, therefore, reason to expect conflicting tendencies in children from divorced homes. The emotional stress, present before and during the divorce, would have diminished, especially with the older children, at the same time as the mother's and children's adaptation in the new environment created new and positive emotional contacts.

The author finally chose the environment of the chronic alcoholic. Only the chronic alcoholic's children could be said, with a high degree of certainty, to have lived under emotional stress so long, that this stress could really be thought to have prejudiced the childrens' mental health.

TEMPERANCE LEGISLATION AND ALCOHOL CUSTOMS IN SWEDEN

Sweden's temperance legislation has its roots in the 16th and 17th centuries, but played a minor role until 1772, when a ban on the distillation of Swedish brandy (brännvin) was introduced. Only a few years later, however, King Gustaf the Third instituted the so-called "Royal Distillaries", i.e. the Crown reserved the right to produce and sell brandy, in order to supplement the national revenue. It was soon possible for private individuals to distil brandy for personal use or for sale, in return for special dues to the Crown.

During the first decades of the 19th century alcoholism was widespread in Sweden. Consumption is estimated as having risen to about 40 litres of Swedish brandy per person annually during this period (cf. Höjer 1955).

The temperance movement came into existence in the middle of the 19th century and chiefly as a result of its work, new legislation was introduced in 1855, by which the right of the individual to distil brandy was abrogated. At the same time, trade in brandy together with other goods, was forbidden.

In 1911, a committee was set up to discuss the question of a total ban on the sale of brandy, which however was never carried into effect. Instead, a bill concerning the sale of intoxicating liquors was enacted in 1917, which largely resulted in a ration of a maximum of four litres of spirit per person per month. The purchases were to be entered in a so-called "pass-book" (motbok). In addition, some years later, total prohibition of the sale of strong beer was introduced.

In 1920, a proposal of total prohibition was laid before parliament, and in 1922, a referendum on this question was held. The majority voted against prohibition and thereby this alternative was dropped once and for all.

The Intoxicating Liquors Act of 1917 remained largely unchanged until the legislation of 1954, which came into force in October 1955 and which is still valid. This meant that the rejection of the "pass-book" system took place at the same time as temperance activity was increased.

It was laid down in a Temperance Law in 1931 that there should be a Temperance Board (Nykterhetsnämnd) in every Swedish community. The function of the Temperance Board was partly, to rehabilitate the alcoholic by various means, and partly, if unsuccessful and if antisocial behaviour was shown, confine him to an institution. This law was replaced in 1954 by the present "law on temperance care".

This law provides that if a person becomes an alcoholic, "measures are to be taken to restore him to a sober life". "Alcoholism exists when a person habitually uses alcoholic drink to the obvious danger of himself or others." If the police, the prosecuting authorities, doctor or certain officials are informated of a case

of alcoholism, it is their duty to report it to the Temperance Board. The Temperance Board must then investigate the nature of the alcoholism and may, if so desired, take supporting or supervisory measures. These apply "when the alcoholic, in consequence of his alcoholism, is found to expose to need or flagrant neglect, those whom it is his duty to support, or otherwise fail grossly in his duties to such persons, or is a burden to the community, his family, or any other person." If such measures do not seem satisfactory, the Temperance Board may arrange for him to be compulsorily confined to an institution for alcoholics by a resolution of the County Council. Finally, the law lays down that the authorities which "deal with the matter in accordance with this law must co-operate with each other. Mutual co-operation must exist between such authorities together with the Board of Guardians and Children's Care Committee ... which carry out social work".

According to the Child Care Laws, now in force, it is incumbent upon the Children's Care Committee, which is to exist in every community to "take care of children who have been subjected to ill-treatment, neglect, or any other danger to health" and "children, who, because of their parents' viciousness, negligence, or inability to bring up children, are in danger of being corrupted". The measures which the Children's Care Committee can take are giving the parents a serious warning, taking steps to supervise the upbringing of the children, or taking charge of the children and placing them in a foster-home or special home.

As has been stated above, alcoholism used to be widespread and serious in Sweden. Is it still of such importance that extensive legislation is required on the part of the community? This question can be answered by giving some current figures as an example.

According to the Royal Liquor Control Board's (Kungl. Kontrollstyrelsen) register, on June 30th. 1958, about ten per cent of men in the 25–50 year age group, had been guilty of one or more of the following misdemeanours: drunkenness, misdemeanour under the influence of alcohol, contravention of the laws and ordinances relating to the production and sale of alcoholic drinks, being admitted to an institution for alcoholics, or placed under the care of the Temperance Board (cf. Collett 1959). On analysing the cases in which the Temperance Board was compelled to intervene in 1957, it was shown that densely populated areas were over-represented compared with the countryside, that unmarried men were over-represented compared with married men, and that women only appeared in isolated cases (3 % of the total) (cf. Grönqvist 1958).

In 1957, the total consumption of alcohol per adult in Sweden amounted to 4.05 litres of pure alcohol, chiefly spirits. This means that the consumption of alcohol was considerably higher in Sweden than in the other Scandinavian countries, in Denmark 3.22 litres, in Norway 2.32, and in Finland 1.72 during the same period (cf. Rögind 1958). Most of the other European countries probably have a higher alcohol consumption than Sweden, but this is chiefly derived from wine (France, Italy, etc.) or beer (Great Britain, Belgium, etc.) (cf. Collett 1957).

EARLIER INVESTIGATIONS

It is well known that environmental disturbances may give rise to mental damage in children. This was described following separation of mother and child by Goldfarb (1943), Spitz (1946), Lewy (1947), Simonsen (1947), Stern (1949), Bowlby (1951), Lewis (1954), Bowlby and others (1956), Ahnsjö (1951 and 1956), Pringle & Bossio (1958), and in association with inadequate homes by Silverman (1935) etc. Children of working mothers are said to show nervous symptoms more often than other children, which has been demonstrated by Hughes (1925), etc., and among Swedish children by Blume-Westerberg (1955). The same is true of the children of women prostitutes which was shown in Sweden by Beskow (1957), etc.

Conversely, its has been shown by many authors, that among children who have behaviour disorders and various adaptation difficulties, similar environmental disturbances appear, in a remarkably high frequency. (Ahnsjö 1941, Gunnarson 1946, Kanner 1948, Nycander 1950, v. Harnack 1953, Jonsson 1956, Curman, Jonsson & Kälvesten 1957, etc.).

In relation to the development of nervous symptoms in children, remarkably few authors have taken up the question of the importance of alcoholism as an environmental factor in the home, in spite of the fact that alcoholism is a relatively common occurrence. In 1946, Gunnarsson found alcoholism in 8.6 % of the fathers of 175 Swedish children with behaviour disorders. In another Swedish series, consisting of 308 children with behaviour disorders, Nycander (1950) reported alcoholism in 8 % of the fathers. Curman, Jonsson & Kälvesten 1957 reported a considerably higher frequency of fathers who were alcoholics. In a group of 200 children with severe behaviour disorders from the treatment home of the City of Stockholm Children's Care Committee (Barnbyn Skå), 44 % of fathers were registered with the Control Board for alcoholism. In a control group of 200 Stockholm children, chosen at random, 18 % of the fathers were alcoholic, according to the Control Board's records.

The majority of psychiatric investigations, which have been published about the children of chronic alcoholics, are largely concerned with genealogical studies of adults.

Pohlisch (1927) investigated the children of 58 chronic alcoholics in Germany, all with delirium tremens. The author's query was whether prolonged alcoholism in the parents damaged the children by genetic transmission. He stated that he had only taken cases "without hereditary abnormality" in order, as much as possible, to include only habitual drunkards. At the time of the investigation the majority of the 156 children examined had become adults. There was no increase in mental morbidity compared with the average population. No cases of psychosis or alcoholism were found, while there were only seven cases of "minor adaptation difficulties".

Panse (1930) described a series of 721 children belonging to 200 German chronic alcoholics. Ninety of the latter were noted as psychopaths. Four of the children had epilepsy, five were idiots, 28 were imbeciles, 75 were feeble-minded, and 38 were psychopaths. A number of these children had been born before the father became alcoholic. These were compared with those born after the father became alcoholic, with regard to the frequency of mental deviation (feeble-mindedness not included). The figure for the former was 10.2 % and for the latter 10.7 %. According to the author, this was against the hypothesis that prolonged alcoholism could cause hereditary damage.

Gabriel (1934), was also unable to find a basis for the development of hereditary damage following prolonged alcoholism. He examined 728 children of chronic alcoholics in Vienna, and showed that "mental symptoms" occurred in only about 10 % of these children. Among "mental symptoms" were included anxiety, night terrors, stuttering, hysterical attacks, motor restlessness, emotional instability and nervous disorders of the heart and stomach. Among the children who were conceived before the father became an alcoholic, the frequency of nervous symptoms was also the same as among those who were conceived after this time. From this, the author concluded that alcoholism in the father had slight importance in the origin of nervous symptoms in the children, but considered that it greatly increased the consequences of "character defects" in the children.

Brugger (1934a and b, 1935) came to a similar conclusion after investigating children of fathers with delirium tremens and chronic alcoholism in Germany and Austria. A series of 967 children of 225 alcoholics, the majority of whom were adult at the time of the investigation, showed 4.5 % feeble-mindedness, 2.3 % imbecility, 5 % psychopathy, and 3 % alcoholism, i.e. more often than in the average population of the district. On the other hand, manic-depressive psychosis, schizophrenia and "hysteria" did not occur more often among children of alcoholics than one would expect. Brugger also demonstrated the same high frequency of oligophrenia and psychopathy among the paternal cousins of the examined children, whose fathers were not alcoholics.

Schachter & Cotte (1950) found that the frequency of oligophrenia was higher among children of chronic alcoholics than among other comparable children. On testing the intelligence of 234 children of alcoholics, "marked mental retardation" was found in 22 % of the cases, but in only 12 % of the 336 controls. A normal intelligence quotient was found in 56 % of the former and 71 % of the latter. From this result, the authors drew the wrong conclusion, that prolonged alcoholism gives rise to hereditary damage.

Animal experiments have not been able to demonstrate that prolonged alcoholism in the fathers conveyed genetic damage to the offspring. (Gyllenswärd 1923 etc.)

In the investigations described above, it is impossible to judge the importance of alcoholism as an environmental factor. All the well-known authors describe a high frequency of psychopathy in alcoholic fathers, and Panse quotes a figure of 45 %. Brugger's investigations showed indisputably that constitutional factors

contribute towards the high frequency of mental abnormality among the children of alcoholics. Furthermore, he was able to show that mental abnormality existed to the same extent among paternal cousins of the children of alcoholics, these cousins not having lived in an alcoholic environment.

Fischer (1950) investigated a series of children from a wine district in Germany. In this series, the frequency of psychopathy among the fathers was not considered to be higher than among a cross section of the German population as a whole. The average wine consumption among adults was given as 3–5 litres per day (7 vol. % alcohol). Even the children drank wine, often from an early age, and only a few per cent of them were wholly abstemious. The series consisted of a sample of 1938 school children, or two thirds of all the school children in the area. On comparison of these children with those from other districts in Germany, not producing wine, no essential differences were shown in physical development, "pathological constitution" (signs of rickets, scoliosis, flat foot etc.), intellectual development or the frequency of psychopathy. The author concluded from this that in spite of the prolonged effect of alcohol on the parents, and their chronic alcoholism, children who were constitutionally unaffected received no physical and mental damage.

This investigation may very well be interpreted as saying that, if a high alcohol consumption in the parents is not complicated by mental insufficiency, there is no risk of damage to the child's physical or mental health.

The results of an investigation by Roe & Burks (1945) also support this idea. The authors compared 36 children of alcoholics with 11 children of psychotics and 25 children of mentally healthy parents, all of whom were put in a foster home before the age of ten, without finding any significant difference between the groups. However, the small size of the series very much limits the value of the findings.

Chronic alcoholism often results in social complications, which, as mentioned earlier, may give rise to nervous disturbances in children. One of the commonest of these complications is, undoubtedly, divorce. Englund (1944) found that the risk of divorce was 18 times greater in families of alcoholics than in families of non-alcoholics in Sweden. Åmark (1951) recorded divorces in 19 % of all families in a series of 203 cases, which were treated at a Swedish psychiatric clinic and institutions. According to Kephard (1944), about 21 % of all divorces in Philadelphia during a particular period of time came as a result of "excessive drinking". Engeset & Idsoe (1958) mentioned divorce in 20 % of cases in a Norwegian series of 244 chronic alcoholics. Wolf (1958) recorded the frequency of divorce in his series from America as being as high as 44 %. Chronic alcoholism also results in reduced ability to work. This and other findings have been pointed out by Ullman, Demone & Sterns (1951), who found that, out of 400 Americans, who were cared for in the poor house on account of their inability to support themselves, 88 % had been guilty of drunkenness at least once. The authors considered that in the majority of these cases, it was alcoholism which made them unable to work.

On the other hand, no modern psychiatric investigation of children from the families of alcoholics has been published. In a work from Germany about alcoholism as a social problem (Keyserlingk 1959), it is pointed out that the most serious risks run by children of alcoholics are those of exposure to sexual interference and assault. This must be borne in mind at the time that alcoholic fathers come for treatment, when considering the care of the children. However, this is only illustrated by a few case-history reports.

Summary

Many authors have shown that environmental disturbances of different kinds may give rise to nervous disorders in the children. However, no psychiatric investigation of the children of alcoholics is available. Genealogical investigations could not establish that prolonged alcoholism caused hereditary damage. On the other hand, it is usually considered that alcoholism results in social complications, particularly divorce.

CHAPTER 2

MATERIAL AND METHODS

Selection of Subjects

By collecting subjects from homes in which the fathers were under continuous treatment in an alcoholic out-patient clinic, it was possible to ensure that the subjects really lived under emotional strain. At the same time, a clear picture of the father and his alcoholism could be obtained from the records kept by the clinic. Without exception, the father's alcoholism had been prolonged, and resulted in all the members of the family being seriously affected by it, in one way or another.

A material such as this, must, of necessity, be a selected one from many points of view.

Thus, those cases of alcoholism which attend the out-patient clinic from which the author took his subjects, differ from those which attend another of Stockholm's alcoholic out-patient clinics, and which were described by Lundquist & Wallin (1957). From the point of view of social groups, this latter series was representative of the whole population of Stockholm. In addition, no case in which a diagnosis of psychopathic personality could be made, was included in the series. Among those cases from which the present author has selected his material however, social group III was heavily over-represented, and there was also reason to suspect that cases of psychopathic personality had been included in the series.

From some points of view it would have been a good thing to have chosen the subjects from chronic alcoholics, who could be said to be representative of habitual alcoholics in Stockholm. By this means, it would have been easier, for example, to judge how important alcoholism itself and its immediate sequelae were for the development of nervous symptoms in the children.

However, in order to achieve the aim of the investigation, it was necessary, as stated above, for the alcoholism to be of such intensity and duration that it really could be expected to constitute an emotional stress factor for other members of the family. On the other hand, where alcoholism of this type was known to exist, it usually brought with it damage to personality, and a fall in social status.

Faced with the choice of material, the author considered it most important to have a guarantee that emotional stress really existed, even if, as a result, it was not fully representative from the point of view of social groups etc.

The subjects have been chosen from the children of male patients who, during the period February 1st–June 15th 1958, were receiving treatment at one of the alcoholic clinics of the Temperance Board

of the City of Stockholm (The Mariapoliklinik).

The Mariapoliklinik is open to both men and women with alcohol problems, and consultation and treatment are free. There is no obligation for the doctors at the clinic to report the patients to the Temperance Board. About one half of the cases come voluntarily, and are not known to the Temperance Board.

Acute cases of alcoholism are normally treated as outpatients, but it is also possible to admit them to the ward belonging to the clinic which have resources corresponding to those found in psychiatric clinics. During 1958, 468 acute cases were admitted, 96 during the day and 372 during the night. Altogether, the number of return visits was 7386.

The non-acute cases are included in a so-called "dispensary clientele" which is under continuous treatment and supervision. The patients present themselves at the clinic at regular intervals for discussion of their problems and medical treatment. In 1958, this clientele comprised 1501 cases. The number of return visits to the clinic was 52,564. The subjects' fathers were selected from this latter group.

There is a certain fluctuation among the dispensary clientele. New patients come from the acute cases and others go away, either because they themselves break off the treatment, or because treatment is completed. During the investigation period February 1st to June 15th 1958, the out patient group fluctuated between 600 and 700 cases, only a few of which were women.

There were two main reasons why only the children of male patients were selected. Firstly, as has been stated, the number of women patients at the Mariapoliklinik is far too small to provide a large group of children, and, secondly, as previously mentioned, the children of women alcoholics are most often taken care of in foster homes, and are therefore not suitable as material for this investigation.

In order to avoid the greatest difficulties in the assessment of the investigation results, a further selection of the material was made. Only children in the 4–12 year age group were included. As the social environment of younger children is extremely limited, the child is too strongly bound to the mother for short observations in a strange environment to have any importance. Furthermore, the stress and other consequences of the father's alcoholism have hardly had time to influence a child before it is four years old to anything like the same noticeable degree as in an older child. The upper age limit has been set to avoid the diagnostic difficulties arising with the onset of puberty, especially considering that it begins in different times in boys and girls (Kinsey, Pomeroy & Martin 1948).

All the male patients in the dispensary clientele at the time of the investigation, having children between the ages of four and twelve years (170 patients with 266 children), were asked if they were willing to allow their children to take part in the investigation. In five cases it was discovered that the children had been placed in a foster home outside Stockholm several years previously. These were excluded from the series, which thus came to comprise 165 families with 261 children.

Selection of Controls

It was considered to be of great importance to find a good control series. In the beginning, it was decided to choose at random a number of controls, of the same age as the subjects, from the census list of the City of Stockholm. By this means a sample would be obtained which was representative of the population in the City of Stockholm in the required age groups. However, because of the bias in the social group distribution among the subjects, such cases were not suitable for direct comparison regarding the frequency of nervous manifestations. With this point in mind, it was considered more suitable to select a "social twin" for each or every other subject and then to compare the subjects and the controls in pairs. By this means, a control series was obtained which was very similar to that of the subjects from the social, sociological and intellectual points of view. In one respect, however, a selection was made. Since it was the children of alcoholics who were to be studied, it was considered justifiable to exclude from the control material all cases whose fathers were registered with the Temperance Board as alcoholics.

The 187 controls were taken only from children on the census list of the City of Stockholm. The controls were chosen in the way described below.

For every subject of school age, a control of the same sex was chosen who went to the same school and was in the same class as the subject, and whose father was in similar employment to that of the subject's father. It was stipulated that subject and control should be born in the same year in order to avoid too great a difference in age. As measurement of intelligence was not to be included in the investigation, a similar level of intelligence was aimed at in the subject and the control. In order to achieve this, children were taken as controls who had the same or similar report total as the subjects (the total of points in the report in all the school subjects except physical training, singing and handwork) at the end of the Spring Term 1958. (According to Husén 1950, there is a rather good agreement between the teacher's judgement and the I.Q.)

The controls of the children of preschool age, were selected from the register of the child-welfare centre. The control was chosen who was listed closest to the subject and who had the same sex, was born in the same year, and whose father had similar work to that of the subject's father. In this way the subject and his control was, in every case, obtained from the same part of the town.

The first case found in the register fulfilling this requirement, or if such a case was not found, the case coming nearest to fulfilling the requirements was taken as the control.

The aim of this investigation was partly to compare the frequency of nervous manifestations in children from homes where the father was an alcoholic with that in children from homes where the father, so far as was known, was not an alcoholic. Because of this, a confidential report on all the control fathers was requested from the Royal Liquor Control Board (Kungl. Kontrollstyrelsen). This showed that in 17 cases, or in 9 % of the total there was a record of alcoholism. The children of this latter group were

therefore excluded from the control series, which finally consisted of 170 children.

Final Series and Investigation Procedure

Twenty four of the 165 families, which made up the subject series, refused to cooperate in the investigation, i.e. about 15 % of the total. The number of children in these families was 32, i.e. about 12 % of the total. The families were a very unsatisfactory selection from the point of view of social co-operation, which must be considered the main explanation of their refusal. Seven of the 24 fathers had been found guilty of criminal activities, and one of them was in prison at the time of the investigation. Five other fathers had been treated, or were being treated in mental hospitals, for psychotic symptoms. In three families the parents had recently separated or divorced. In one family, both the father and the mother were attending the Mariapoliklinik. Seventeen of the 32 children were at school. The teachers described 13 of these children as obvious problem children. Of these, two had shown asocial characteristics, one of them pilfered, the other pilfered and had also been guilty of repeated arson.

As a result, the investigation finally consisted of 141 subject families, or 229 subjects in all.

In the control series, five children, or 3 % of the total, refused to co-operate in the investigation. Moreover, two cases were no longer accessible after the selection because they had moved from Stockholm. The control series, finally included in the investigation, consisted therefore of 63 children.

The examinations, which usually took place in the Psychiatric Department at K.L.B., comprised both an interview with the mother and a physical and psychiatric examination of the child.

Some of the interviews and examinations had to be carried out at home, because the mother could not or would not present herself at hospital. This occurred in eight subject, and ten control families. Many of the parents, particularly among the subjects, could be made to co-operate only after intensive persuasion, by personal visits to the home and by telephone conversations.

The child was usually accompanied to the examination by the mother. Only one of the subjects was accompanied by the father, and this was because the mother was in a mental hospital at the time of the examination. A few of the children in both groups were accompanied by both parents.

The examination of the subjects took place during the period February 1st to June 15th 1958, and of the controls, during the period 15th. September to 15th. December 1958, the interval being about six months. When assessing the information received, this interval was taken into consideration. Thus in the case of the controls, information about events which occurred during this interval was not recorded.

Since it was the mother who answered the questions in all cases except one, there was an opportunity of studying her state of mental health at the time of the investigation.

On the other hand, it was not the author who undertook the assessment of the state of mental health of the fathers. This was done at the Mariapoliklinik by the

doctor on duty. The father's alcoholic habits, behaviour under the influence of alcohol and his social adaptation were recorded according to a scheme drawn up beforehand. It was further noted whether he had been in a mental hospital or alcoholic institution or whether he had served a prison sentence, and finally, whether or not he was capable of looking after his family. There were entries in the Control Board's register for all the fathers. The case histories from the Mariapoliklinik were placed at the disposal of the author.

The interview with the mother usually took place in a private room with the author, while the child was kept busy in the psychologist's room or in a waiting room. The interview consisted of questions on the family's physical and mental state, on home conditions, and, in particular, on the father's alcoholic habits and his behaviour under the influence of drink. The discussion extended to pregnancy and delivery, the child's infancy and early development, the child's physical and mental state, and ability to adapt itself at home, at school and among his companions. Particularly careful enquiries were made as to whether the child had previously been medically examined or treated in hospital.

The case histories have chiefly been drawn up according to a questionnaire worked out by Schmeer & Klüwer (1950) for the scientific assessment of childrens' neuroses. This questionnaire, modified according to Bennet (1953) had been previously tested by the author in an investigation of children who had had aseptic meningo-encephalitis (Müller, Nylander, Larsson, Widén & Frankenhaeuser 1958). There were no difficulties in the evaluation of the answers with regard to the information on the physical condition. Such was not the case with regard to the information about the state of mental health. Many of the original questions about mental symptoms seemed to elicit answers that were too subjective or too weak for scientific assessment. Lapouse & Monk (1958) tried in an investigation to test the reliability of the information, which mothers gave about their children's mental state. They found a relatively high degree of reliability with such symptoms as could be demonstrated objectively or which could be easily distinguished from normal behaviour. As regards all the other symptoms they thought the degree of reliability poor. In the questionnaire used by the author (see Appendix), almost all the questions included could be answered with concrete examples. (Has the child visited a doctor or been treated for nervous disturbances? Has the child shown symptoms of enuresis, sleep disorders, speech defects, difficulty with companions, etc.?)

The physical examination was carried out after the interview, with the mother always present, so that the child would not be unnecessarily upset.

Some idea of the child's mental state was obtained during the physical examination, and the undressing. This picture was later supplemented by conversation with the child. Only in a few cases were the children so frightened that no contact at all could be established. The psychiatric examination did not include any special psychological or psychometric tests, since the results of these were not thought to elucidate the inquiry.

When there was reason to suppose, that some subjects' mothers would suspect

that the investigation was carried out at the instigation of the child care authorities, and then because they were afraid of proceedings by them, could be thought to withhold information important to the case history, particularly great emphasis was laid on trying to obtain some form of objective record in as many cases as possible.

For this reason the child's teacher was contacted in all cases where the child attended school. The teacher was asked about the child without any reason for the inquiry being given. The questions concerned firstly, whether or not the child could keep up with the class academically, and, secondly, whether or not the child's behaviour otherwise differed from that of the average child.

It was more difficult to obtain objective case histories of the children in the pre-school age group. In those cases where the children were examined at the child-welfare centre, reference was always made to the case histories kept there. By this means, the information given by the mother about the child's early development and state of health could be checked.

In all the cases where the child had visited a doctor or been treated in hospital, either the hospital records were studied, or the doctor who had examined the child was approached in person for information.

By means of checking the Child Care Committee's register, information was obtained about whether the child had been taken into care and protective upbringing, and about the reason for this, or whether or not the attention of the committee had been directed to the child as a result of anti-social behaviour.

In a similar way, a check was made as to whether or not the child had attended one of the city's child-guidance clinics, by studying the register kept by these clinics.

Finally, home visits were made to about 20 families from each group, in order to check some uncertain data in the case records.

It is clear from the above that various attempts were made to verify the information given by the mothers. It appeared that the mothers' histories agreed closely with the information obtained from public records and documents about the child. However, this was not so in the case of the father and his alcoholism. Only exceptionally was information about the father's alcoholism in full agreement with that which was recorded in the case history of the father at the Mariapoliklinik.

In order to obtain an idea of the reliability of the history given by the subjects' mothers, the author proceeded as follows.

After collecting case histories the frequency of nervous manifestations was compared between the subjects who were stated to have siblings with nervous symptoms and those whose siblings did not have such symptoms. If some mothers had withheld information about the subjects, it was reasonable to assume that they might also have done so in the case of the siblings. In other words, those subjects who had siblings with nervous symptoms ought also to have nervous symptoms, while those who had siblings without nervous symptoms, should, themselves, be symptom-free. However, this was not the case, since the frequency of nervous manifestations was largely the same in both groups of subjects.

The Size of the Material

In sampling investigations, in which the absolute or relative frequency of units in the population belonging to a certain sub-group is to be estimated, one can proceed in the following way (Björk 1954).

If n units are taken out of a population of N units by "unlimited random selection", the mathematical expectancy of p = P.

The error of the mean for p is:

$$\sigma p = \sqrt{\frac{N-n}{N-1}} \cdot \sqrt{\frac{P \cdot Q}{n}}$$

and the relative error of the mean for p is

$$\frac{\sigma p}{P} = \sqrt{\frac{N-n}{n-1}} \cdot \sqrt{\frac{Q}{n P}}$$

The size of the sample n needed for the relative error of the mean p to reach a definite size k may be obtained from the following equation:

$$n = \frac{N Q}{K^2 P (N-1) + Q}$$

This formula has been used on the material of the Temperance Board in Stockholm. Every year this material consists of about 400 breadwinners with children subject to proceedings according to 15§ of the Temperance Law (supervision). The number of children (N) may be estimated at about 800. P and Q are unknown. On alternative estimation of P (P = 0.2–0.4–0.6) and Q respectively (Q = 0.8–0.6–0.4) and with the relative error of the mean of p at 10 % (k = 0.1), the size of the material is alternatively 265, 125 and 62 cases.

The alternative to be selected depends on which P is considered most likely. If the group of children in touch with the Temperance Board is fixed at 125 there is scope to distribute the material according to age.

On selection of the subject material, this group consisted of 154 cases.

For the other two groups, the cases not registered with the Temperance Board and the controls, it is more difficult to make an estimate of the size of the sample. For example, according to the method previously used, it is necessary to select a considerably larger sample of controls than of Temperance Board subjects, since the sampling ratio is inversely proportional to the frequency (P).

For practical reasons, the controls consisted of 163 cases which involved a certain arbitrariness.

The group of non-Temperance Board cases would conveniently consist of 100 cases according to the above. In fact, there were only 76 cases.

Statistical Methods

The following methods were used for the statistical treatment of the material.

The error of the mean for the percentage values, $\varepsilon(p)$, was estimated according to the formula:

$$\varepsilon(p) = \sqrt{\frac{p(100-p)}{n}},$$

where p is the percentage and n the number of cases in the material.

N = total number of units in the population
A = NP = number of units in the population which belong to a particular sub-group
Q = 1–P
n = number of units in the sample
a = np = number of units in the sample who belong to a sub-group

The error of the mean of the difference $\varepsilon(D)$, was estimated according to the formula:

$$\varepsilon(D) = \sqrt{\varepsilon_1^2 + \varepsilon_2^2},$$

where ε_1 and ε_2 were the errors of the mean for the respective percentages.

The comparison of presenting symptoms in the subjects and controls was made with the help of a sign-test. The test was applied to the group of subject-control pairs where the symptoms had occurred only in the subject or only in the control, when the hypothesis that the symptom occurs as often in subjects as in controls was tested with the help of table 10a in Dixon & Massey (1957). Groups with less than eight subject-control pairs were not studied.

For the number of children per family and the points total in the report, comparison was made between subjects and controls using a t-test. For each subject-control pair, the difference d between the subject and control, and the value of t were estimated.

$$t = \frac{\bar{d}}{S_d/\sqrt{n}}$$

$\bar{d}$ is the mean of the differences d, n the number of differences and s_d the scatter of the differences.

$$S_d = \sqrt{\frac{\varepsilon(d-\bar{d})^2}{n-1}}.$$

The significance of t was judged according to the table of t-distribution (Dixon & Massey).

Comparison between the number of symptoms per case in the different subject groups was made by the t-test, where the value of t was estimated in the following way:

$$t = (\bar{x} - \bar{y}) \sqrt{\frac{(n_1 + n_2 - 2)\, n_1 \cdot n_2}{n_1 + n_2 \left[\varepsilon(x-\bar{x})^2 + \varepsilon(y-\bar{y})^2\right]}},$$

where x denotes the number of symptoms per subject in one group, y the corresponding number in the other group, while n_1 and n_2 are the number of cases in the groups respectively. The significance was obtained from a table of t-distribution (Dixon & Massey).

The following definitions of significance have been used:

0	$5\,\% < p$	: no significant difference
*	$1\,\% < p \leqslant 5\,\%$	: almost significant difference
**	$0.1\,\% < p \leqslant 1\,\%$	: significant difference
***	$p \leqslant 0.1\,\%$	: highly significant difference,

where p denotes the probability that the difference was caused by chance.

CHAPTER 3

THE SOCIAL AND MEDICAL STRUCTURE OF THE MATERIAL

Sex and Age Distribution

Altogether there were 229 subjects (113 boys, 116 girls), and 163 controls (83 boys, 80 girls). Both series are shown in Table 1, divided up according to sex and age.

From the table it can be seen that the number of boys is almost the same as that of the girls in both series, and that on the whole, the distribution of the different age groups is even. The age differences between the subjects and the controls on matching, is shown in Figure 1. On the positive part of the division those pairs where the control is the older are given, while on the negative part, those cases where the subject is the older are illustrated. As can be seen, the age difference in every case is less than 12 months. In 129 cases, 79 % of the total, the difference does not exceed six months. The subject is the older in 86 pairs, the control in 77.

Summary

On the whole, the material is evenly distributed in relation to sex and age. In 79 % of all the pairs, the age difference between subject and control does not exceed six months. In about one half of the cases the subject was the older, in the other half, the control.

Social-Group Distribution

In Table 2, the case material has been divided up into social groups according to the 3-degree scale which is used in the official Swedish statistics. For comparison, the voters at the 1956 election for the Second Parliamentary Chamber in the City of Stockholm are divided according to the same principle. The cases have been allotted social groups in relation to the work of the father. Usually the work recorded is that which the father had on the day of investigation. In those cases where

TABLE 1. *Subject (S) and Control (C) series grouped according to age and sex.*

	Age in years																					
	4		5		6		7		8		9		10		11		12		Total	
Sex	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
Boys	9	6	17	13	10	9	14	10	10	8	10	6	13	10	11	9	19	12	113	83
Girls	7	4	8	8	12	11	11	7	13	10	15	9	17	14	12	8	21	9	116	80
Total	16	10	25	21	22	20	25	17	23	18	25	15	30	24	23	17	40	21	229	163

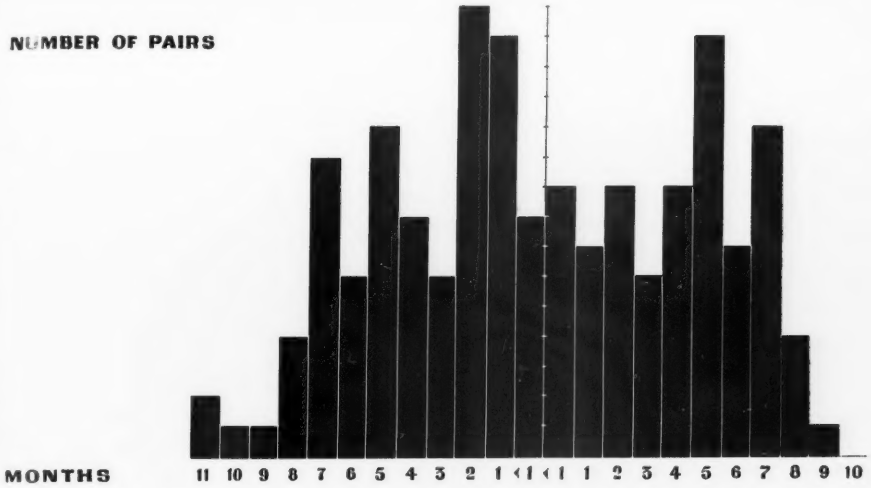

Fig. 1. The age difference in months between subjects and controls, showing the number of pairs in each monthly interval. (Controls older = to the right. Subjects older = to the left.)

the father was unemployed, the work recorded is that which the father had most recently held.

The table shows that the greater part of the material (83 %) has been taken from social group III. This is because most of the Mariapoliklinik patients come from that group. Many of the fathers have difficulty in continuing their work, generally because of their alcoholism. According to information obtained from the mothers, changes both in jobs and places of work occur frequently. This situation has in many cases brought with it inferior terms of employment, and worsened social status. However, only in isolated cases has this caused a fall from one social group to another.

It is remarkable that in 23 cases, or 16 % of the total, the father's work was stated to be that of car- or lorry-driver (cases 1, 5, 7, 10, 18, 20, 26, 36, 45, 49, 74, 84, 97, 98, 99, 107, 109, 111, 122, 129, 132, 135, and 138). According to the Statistical Year-Book of Stockholm (1958), in 1950, there were 11,077 car- or lorry-drivers in the City of Stockholm, comprising about 5 % of all male workers. It could be said

TABLE 2. *Social grouping of subjects in relation to that of voters in the City of Stockholm at the 1956 election.*

Social group	Subjects		Voters	
	Boys	Girls	Men	Women
I	3 (3%)	1 (1%)	32,676 (13%)	29,250 (10%)
II	13 (12%)	21 (18%)	100,382 (40%)	152,102 (50%)
III	97 (86%)	94 (81%)	116,314 (47%)	122,178 (40%)

that it is because a car- or lorry-driver is forced, by the laws governing sobriety while driving, to seek medical advice during the early stages of alcoholism, that so many workers in this field are found among the fathers. However, among the material, no significant difference could be established between car- or lorry-drivers and other workers, regarding the duration and type of alcoholism.

As a rule it was possible to choose controls whose fathers had the same jobs as those of the corresponding subjects. "The same job" is intended to indicate that the jobs had the same character. Thus unskilled labourers have been grouped together with unskilled workers generally, without giving exact details of the nature of the work. In the same way, builders have been compared with plumbers, and junior office workers with junior office workers, independent business-men with independent business-men etc.

In 25 pairs, however, agreement such as this could not be reached. With regard to the father's work in eight cases, the subjects' fathers belonged to a higher social group than the controls' fathers (cases 2b, 8, 32b, 42, 46, 68b, 110a, and 110c). On the other hand, the subjects' fathers belonged to a lower social group in ten cases (cases 49a, 57a, 57b, 58, 66, 70c, 81b, 102a, 104, and 126a). In the other seven pairs the fathers belonged to the same social group, despite a difference in the type of work.

The pairs have been matched according to the social group of the subjects.

Summary

The greater part of the subjects (83 %) belonged to social group III, because most of the patients at the Mariapol li-nik come from this social group. Ther is a predominance of car- or lorry-driv rs among the fathers, amounting to 16 %. The majority of the fathers in both groups have had the same work, but this was not so in 25 cases. The differences are discussed.

The State of Mental Health and the Occurrence of Alcoholism in the Paternal and Maternal Grandparents

In the questionnaire used were questions on the state of mental health of the grandparents. Detailed information could not be obtained. All that were recorded were mental illnesses and symptoms of such a degree of severity that either hospital care or prolonged medical treatment was required; difficulties of social adaptation of such a severe degree that they diminished wage-earning capacity; and chronic alcoholism. If alcoholism was reported, it was, as a rule, accompanied by difficulties in social adaptation. Because of this, in the account which follows, only alcoholism is mentioned in these cases.

Since these questions concerned the misuse of alcohol it would have been desirable to have had certain criteria on what was meant by this expression. However in practice it proved to be quite impossible to do this. In many cases the mothers could only give the information that alcoholism had existed, without being more precise. It appears likely that in the majority of these cases it was indeed a question of chronic alcoholism. Those cases which were reported as occasional drinkers were not counted as alcoholics, in spite of the fact that among them there were probably several who were alcoholics.

The subjects' parents, especially the fathers, had in several cases been born out of wedlock, grown up in a childrens' home, or been separated from their homes early in life. In these cases, no information about the grandparents could be obtained.

The reliability of the information given could not be checked. Indeed, in many cases the mothers did not appear to know much about either their own, or their husbands', parents.

Thus it may well be said that the frequency figures on mental illness and alcoholism discussed below are minimal.

Among earlier investigations Ellerman (1948) in a Danish series, has shown that 28 % of chronic alcoholics had alcoholic fathers. Åmark (1951), in a Swedish series, found that the incidence of alcoholism among the fathers of alcoholics was about 26 %. Engeset & Idsoe (1958), in a Norwegian series, found that 42 % of alcoholics came from homes, where one or both parents were alcoholics.

In the author's series of subjects, alcoholism occurred among the paternal grandfathers in 46 cases (33 % of the total), and among the paternal grandmothers in three cases (about 2 % of the total). Of these 49 cases several had been patients in mental hospitals, and one had committed suicide while under the influence of drink. In addition, one of the paternal grandfathers and one of the paternal grandmothers, were insane. Both of these had received treatment at a mental hospital, but the symptom-picture was not known. Finally, one of the paternal grandmothers revealed that she had not learned to talk before she grew up. Among the maternal grandparents there was one case of alcoholism, one of imbecility, and one of prolonged mental insufficiency, possibly a severe anxiety neurosis.

Among the controls' grandparents, only one case of alcoholism was recorded. The others had not required treatment for mental illness, or been alcoholics.

Summary

Alcoholism was found in 33 % of the subjects' paternal grandfathers and in 2 % of the paternal grandmothers. In the subjects' maternal grandparents together with the controls' grandparents, only occasional cases of mental illness requiring prolonged treatment, or of alcoholism, were mentioned.

Alcoholism, Social Adaptation and State of Mental Health in the Fathers

The information about the subjects' fathers, concerning alcoholism, social adaptation and state of mental health, was obtained from the case-histories taken at the Mariapoliklinik. The corresponding information, concerning the controls' fathers, was given to the author by the mothers.

It was stated that alcoholism did not exist among the controls' fathers, while, as is clear from the conditions of the investigation, all the 141 subjects' fathers were chronic alcoholics. The kind of alcoholism that they had is described below.

The duration of the alcoholism was less than five years in 22 cases, five to ten years in 57 cases and over ten years in 62 cases.

It occurred daily, or almost daily in 89 cases, sporadically (usually at the end of the week) in 29 cases and periodically (periods of at least four days) in 23 cases.

The type of intoxication in 66 cases was

noted as average, and in 75 cases as grossly disturbing.

The Temperance Board had been notified in 97 cases (69 % of the total), while 44 cases (31 % of the total) were not known by the Board. Of the former group, 46 cases were undergoing treatment at the time, i.e. they were under the supervision of the Temperance Board, or were receiving other kinds of help.

Seventeen cases (12 % of the total) had been in-patients at an institution for alcoholics.

The number who had been convicted was 28 (20 % of the total). In one half of these cases, the charge was one of drunkenness while driving. The other cases concerned larceny (5 cases), burglary (2 cases), forgery (2 cases), assault (1 case) and carrying dangerous weapons (1 case). In three cases the nature of the crime was not known. None of the controls' fathers had been convicted.

In 22 cases (16 % of the total) the subjects' fathers were not capable of supporting their families, the latter being entirely dependent on the earnings of the mothers or on the Public Assistance Board[1]. The controls' fathers were all in employment and capable of supporting their families.

The state of mental health in all the subjects' fathers was noted as less than satisfactory. Mental deterioration had been demonstrated in 30 cases (21 % of the total). "Dementia" was used to describe 12 of these cases from the Mariapoliklinik, "epileptiform symptoms" nine cases, "psychotic symptoms" seven cases, and "oligophrenia" two cases. Symptoms of mental insufficiency were recorded in 15 cases (9 % of the total) among the controls' fathers. Of these, seven also had ulcer symptoms and were receiving medical treatment, while two had been operated. In addition, there was one case of gastritis. All these eight cases had nervous symptoms periodically, in the form of irritability, tiredness, sleeplessneess, etc. In three of the 15 cases mental illness actually existed, in one, anxiety neurosis, in another, depression, and in the third, atypical insufficiency. Three cases had previously had periods of mental illness, but at the time of the investigation were, on the whole, healthy. One of them had been an in-patient at a mental hospital. Finally, in one case, the father had had repeated attacks of an epileptic type and, at the time of the investigation, was undergoing examination in hospital, and was also depressed.

In comparison it may be stated that Inghe (1958) found that 14 % of a control series, with a division of social groups largely similar to that in the present material, comprising 166 men, aged 16–67 and living in Stockholm, were in need of medical treatment for nervous symptoms.

[1] Socialvårdsnämnden.

Summary

In many of the subjects' fathers alcoholism had persisted for a long time (in 44 % for more than 10 years) and had recurred daily (in 63 % of cases). Intoxication had been grossly disturbing in 5[illegible] % of cases. About two thirds of the cases had been reported to the Temperance Board, while about one third was not known to them. In many cases the social adaptability was poor. Twelve per cent of the cases had been in-patients in institutions for alcoholics, 20 % had been convicted

and 16 % were incapable of supporting their families. Among the controls' fathers, alcoholism did not occur and the social adaptability was good throughout. The state of mental health among the subjects' fathers was, in every case, less than satisfactory, and in 21 % a mental deterioration was present, often in the form of early dementia. Among the controls' fathers 9 % had, or had recently had, such pronounced mental symptoms that they were forced to seek medical advice, while the rest appeared to be in normal mental health.

State of Mental Health in the Mothers

At the time of the investigation, 45 of the 141 subjects' mothers (32 %), and 17 of the 163 controls' mothers (10 %) were diagnosed as mentally insufficient. The difference is highly significant (22 ± 4.6). Seven of the subjects' mothers were considered constitutionally asthenic, and six as mentally retarded.

The kind of mental insufficiency is set out in Table 3.

From this it can be seen that the increased frequency of mental insufficiency can be localised to the groups "worn-out mother" and depression respectively.

About half of these mothers were classified as "worn-out mother", i.e. they appeared tired, resigned, and subdued without showing definite signs of mental depression, but this was so in only one of the controls' mothers. The latter had had a legal abortion together with sterilisation some years previously.

Mental depression with psychomotor inhibition was found in ten (7 %) of the subjects' mothers and four (2 %) of the controls' mothers (difference 5 ± 2.4).

An atypical symptom picture occurred in three cases of both series. Two of these in the subjects' series were alcoholics. At the time of the investigation one was in a mental hospital, admitted in delirium tremens and the other, besides being alcoholic, was probably also a drug addict. This case is described in detail below.

Case 107: The family consisted of the parents and five children, aged 8, 6, 4 and 3 years, and eight months respectively. On a home visit 14.4.58., the mother was at home, the father was reported to be at work and the children were in the fever hospital with scarlet fever, having been recently taken

TABLE 3. *Mental state in insufficient mothers of subjects and controls.*

Kind of insufficiency	Number of cases	
	Subjects	Controls
"Worn-out mother"	24	1
Depression	10	4
Anxiety neurosis	3	6
Neurosis with predominantly hysterical symptoms	3	3
Obsession-compulsion neurosis	2	0
Atypical symptom picture	3	3
Total	45	17

into the care of the Childrens' Care Committee for placing in a foster home. When visited the mother was extremely drunk, dressed in rags and had a flesh wound on one arm. The home was neglected. In the beginning she was aggressive, but she later broke down, cried, and stated that she also took amphetamine and morphine. During the day she loitered in the streets and went with men who had alcohol. She had been arrested by the police five times recently. After one such arrest she attempted suicide. She declared that she very much wanted a divorce, but that she did not dare discuss it since her husband had threatened her with a knife.—Furthermore, during the home visit another drunken woman was found in the flat. She had a "black-eye", which she claimed to have received from a blow in the face by her own husband.

In the control series, a mother with atypical symptoms had received deep X-ray treatment after a brain tumour operation, and was almost demented. None of the controls' mothers admitted to being alcoholics.

Only one of the subjects' mothers was undergoing medical treatment, viz. the woman who was in a mental hospital with delirium tremens, while ten of the mentally insufficient mothers in the control series, i.e. over half of these were receiving medical treatment regularly.

In four of the control families both father and mother were said to have symptoms of mental insufficiency.

In a control series with division into social groups largely similar to that of the present subjects' series, consisting of 334 women, 16–67 years of age, and living in Stockholm, Inghe (1958) found that 10 % of the total required medical treatment for nervous difficulties. This corresponds with the author's findings among the mothers in the controls' series.

Summary

Mental insufficiency was considered to exist in 32 % of the subjects' mothers' and 10 % of the controls' mothers. The difference is highly significant. Among the former the most common symptom was of the type "worn-out mother" or depression, while among the latter these were found in only a few cases. Alcoholism was found twice in the subjects' series, but not at all in the controls' series. One of the subjects' mothers was under treatment for nervous symptoms, while over half of those controls' mothers who were mentally insufficient were receiving treatment for similar conditions.

The Mothers' Employment

The mothers were working in 73 families of the subjects' series (52 %) and 58 families of the controls' series (36 %). The difference is statistically significant (16 ± 5.6). It may be stated in comparison that according to the Statistical Year-Book of Stockholm 1958, compiled in 1950, the number of married women in employment was 29.95 % of all the married women in the City of Stockholm.

Of these, 41 subjects' mothers (29 %) and 20 controls' mothers (12 %) worked full-time outside the home, while 32 subjects' mothers (23 %) and 38 controls' mothers (23 %) worked half-time.

Thus the frequency of mothers working half-time was the same in both series, but full-time employment outside the home was found more than twice as often among the subjects' mothers as among the controls' mothers. The difference is highly significant (17 ± 4.5). This is probably explained by the fact that the subjects'

TABLE 4. *Siblings of subjects (S) and controls (C), grouped according to age and sex.*

	Age in years															
	<4		4–6		7–9		10–12		13–15		16–18		>18		Total	
Sex	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
Boys	17	22	—	15	—	19	—	33	12	14	8	14	14	3	51	120
Girls	15	20	—	14	—	17	—	18	14	22	11	12	5	4	45	107
Total	32	42	—	29	—	36	—	51	26	36	19	26	19	7	96	227

mothers were compelled to shoulder the burden of supporting the family to a greater extent than the controls' mothers. About 16 % of the subjects' fathers were not able to support their families, while all the controls' fathers were employed and capable of supporting their families.

Summary

The frequency of mothers with full-time employment outside the home was more than twice as high in the subjects' series than in the controls' series, and the difference is highly significant. On the whole, this is considered to depend upon the fact that the subjects' mothers had to bear the main burden for supporting the family to a greater extent than the controls' mothers.

The Number of Children Per Family and the Sex and Age of the Siblings

In the subjects' families, there were 96 other children in addition to the subjects (51 boys and 45 girls). They were not included in the subjects' series because of their age, i.e. they were younger than four years or older than 12 years. These cases are shown in Table 4, together with those of the controls' siblings, viz. 227 cases (120 boys and 107 girls) divided up according to sex and age.

It is seen from the table that the subjects' siblings were, in about one third of cases, younger than the subjects, and in two thirds, older. The controls' siblings on the whole, were distributed equally among the various age groups up to and including the 16–18 years group. In the oldest age group there were more subjects' siblings than controls' siblings, both absolutely and relatively.

In the subjects' series, the average number of children per family was 2.3, while in the controls' series it was 2.4. In the random census in Sweden in 1936, the average number of children per marriage with children was 2.41 in towns (cited Gyllenswärd 1946).

When choosing the controls, the number of children per family was not taken into consideration, as has been set out above. It would, naturally, have been convenient to compare only-children with only-children, the youngest child with the youngest child, etc. This was not feasible, however. The above requirements alone in the choice of controls produced great difficulties in the finding of suitable so-called "social twins", especially with regard to school children, who made up about two thirds of the entire series. Considering that the opinion of the teacher would be used in assessing the childrens' state of mental health, it was considered necessary to

TABLE 5. *Symptom-picture in siblings of subjects (S) and controls (C).*

Kind of symptom	S-siblings ♂	♀	♂+♀	C-siblings ♂	♀	♂+♀
General symptoms of nervousness	4	3	7	3	2	5
Enuresis	3	1	4	3	0	3
Tics	1	1	2	0	0	0
Headache	0	2	2	0	0	0
Abdominal pain	0	0	0	3	0	3
Stuttering	0	1	1	1	0	1
Sleep disorders	3	0	3	1	0	1
Depression	1	0	1	0	0	0
Obsession-compulsion symptoms	0	1	1	2	2	4
Unsociability	2	0	2	0	0	0
Peptic ulcer	2	0	2	0	0	0
Hysterical attacks	0	1	1	0	0	0
Established oligophrenia	2	0	2	2	1	3
Total	18	10	28	15	5	20

choose the controls from the same class as the subjects in order to obtain a uniform and fair judgement.

In the subjects' series there were often several children from the same family, which was not the case in the randomly chosen controls' series. Thus 70 % of the children in the subjects' families were included in the investigation, but only 42 % of those in the controls' families. This implies, for example, that five subjects who came from the same five-child family, could be allotted controls from five one-child families. It follows that the subjects, therefore were, on the average, drawn from larger families than were the controls. The distinction is insignificant, however. A difference is made of 0.3 children per family ($1\ \% < p \leqslant 5\ \%$).

Summary

The number of children per family was about the same in both series, 2.3 in the subjects' series and 2.4 in the controls' series. Because a greater proportion of subjects' family children took part in the investigation than those of controls' families, the subjects were drawn on the average from somewhat larger families than the controls.

The State of Mental Health in the Siblings

Nervous symptoms were found in 28 of the subjects' siblings (18 boys and 10 girls—29 % of the total) and in 20 of the controls' siblings (15 boys and 5 girls—9 % of the total). The nervous symptoms in both series are set out in Table 5.

All the subjects' siblings with nervous symptoms, except one three-year-old boy with a sleep disorder, were over 12 years old, i.e. 27 cases (28 % of the total).

Only five of the controls' siblings with nervous symptoms were over 12 years old, i.e. 2 % of the total. The difference is highly significant (26 ± 4.6). Two of the controls' siblings were under four years old.

Of the 13 symptoms recorded in Table 5, 12 were found among the subjects' sib-

lings, but only seven among the controls' siblings.

The subjects' siblings, in general, also showed more serious mental symptoms than the controls' siblings. Of the former, two boys had been placed in detention home,[1] and taken into protective custody for unsociability, one boy had received out-patient treatment for depression several years previously, and one girl had been an in-patient in the child-psychiatric ward. A further three cases received treatment for nervous difficulties, all at the child-guidance clinic. Two boys were stated to have peptic ulcers and nervous symptoms, both having been in hospital. Of the controls' siblings, six (4 boys and 2 girls) had been to the doctor with nervous symptoms, but none had been in hospital or placed in an institution.

Summary

The frequency of nervous symptoms among the subjects' siblings, who by reason of age, were not included in the series, and the controls' siblings, was 29 % and 9 % respectively. The information given by the mothers indicated that the subjects' siblings in general had more serious mental symptoms than those of the controls.

Other Home Conditions

In 39 of the subjects' families (28 %) there had been a divorce. This was significantly higher than in the controls where divorce occurred in only six families (4 %). The difference is highly significant (24 ± 3.9). Of the remaining subjects' families, the parents lived together, in one case unmarried. In a number of the subjects' families, divorce had been filed during the previous two years, and only in five cases had the separation occurred earlier (cases 20, 29, 39, 127, and 139). In every case the reason given was the father's alcoholism, as the direct or indirect cause. In one case the father had committed suicide the night before the investigation. This case is described below.

Case 70: Home visit 7.6.58.: The family consisted of the mother and four children, aged 12, 10, 9 and 6 years. Flat with two rooms and kitchen. The father, a builder, had been an alcoholic for more than ten years, was often drunk, aggressive, brutal and threatening at home. He was pathologically jealous of the mother and especially disturbing at night. On the night of 7.6.58. he came home extremely drunk, banged on the windows and demanded to come in, threatening to take the mother's life. However, she did not admit him but instead sent for the Flying Squad. When the police arrived the father had already disappeared, but was later found in a park, having hanged himself.

Two homes in the control series were incomplete due to the fathers' death from organic disease.

Among the subjects a number of other homes were broken up in addition to those discussed above. Divorce had earlier been filed in six cases, but the parents had later come together again, in every case, according to mothers, due to threats or pleadings on the part of the fathers. In a further eight cases the mother wanted a divorce, but either because of fear of the father, or because of the mother's inability to support both herself and the children, it had been postponed. Here are some illustrative case-histories:

Case 69: The family consisted of the parents and three children, aged 17, 14 and 10

[1] Ungdomsvårdsskola.

years. The father had been a bad alcoholic for about ten years. He was found to be aggressive, brutal and disturbing at night, besides leaving money only sporadically for the family's maintenance. In order to support the family, the mother had to find employment outside the home and for several years had worked as a cleaner in three different places at night-time. She, herself, slept for some hours on an office sofa, sometimes here, sometimes there. She had thought of divorce, but not until the children were older, so that they could look after themselves.

Case 137: The family consisted of the parents and two children, aged four years and four months respectively. The father had been a bad alcoholic for more than ten years, and was found to be aggressive and brutal. The parents separated in 1953 and in 1957, but after a short time came together again, since the father begged for this and the mother could not support herself. The father had lately deteriorated, breaking up the furniture, and was found to be unmanageable. The mother was now definitely considering divorce, but was uncertain if she dared go through with it.

In 25 cases, the mother had not considered divorce, despite the father being described as aggressive and brutal in the home, often threatening the mother and children. Here are some examples:

Case 17: The family consisted of the parents and three children, 14, 12 and 7 years old. The father had been a bad alcoholic during the whole marriage, and often appeared drunk, aggressive and brutal. He sometimes threatened the mother and children with an axe, screaming and yelling.

Case 21: The family consisted of the parents and one child, aged seven. The father had been an alcoholic during the whole marriage, always appeared very aggressive while under the influence of drink, often threatened to kill the mother and child so that they dared not stay at home, but were compelled to stay overnight with friends or at a hotel.

Similar circumstances were not once described in the control series.

For comparison the unpublished investigation of Curman, Jonsson & Kärvesten (cited in Official State Reports 1957: 40) showed that 13 % of 222 randomly chosen Stockholm boys, aged 8–16, came from a divorced home.

In about 20 % of cases the home conditions were assessed after a home visit, while the others were assessed from the history alone. In both series, they were of the accepted standard for the country. A telephone and radiogram or television set were found in the majority of homes. Only in one case could a subject's home be considered unsatisfactory. An account of this is now given.

Case 46: The family consisted of the parents and two children, four years and one year old. For some years, the family had lived in one of a group of cottages in a town park. The cottage was not protected against the winter, so that the wind and rain came right inside. The floor area was about 20 m². In winter it was impossible to keep the inside temperature normal, however much the cottage was warmed and it was necessary to keep on one's outdoor clothes inside the cottage. The children suffered from frequent upper respiratory tract infections. The neighbourhood was disturbing. In the group of cottages adjoining, there were often alcoholics about during the day and when the children went out, they often bumped into drunken men and women.

Among the controls' families, there was only one home that was not modern. The homes that were visited were, almost without exception, well looked after.

With only one exception (see case 107, p. 31) both mothers and children were well dressed and well cared for.

Summary

There had been a divorce in 28 % of the subjects' families and in 4 % of the controls' families (difference 24 ± 3.9). A further 4 % of the subjects' families had petitioned for divorce, but had come together again after a short separation. The home conditions were good in both series, with a few exceptions among the subjects' families.

Illegitimate Births

There were 24 cases of illegitimacy (15 boys and 9 girls—10 % of the total) in the subjects' series. The parents of one family had lived together unmarried for several years, but the remainder had married after the first delivery. Only one boy was born illegitimate in the controls' series.

According to the Statistical Year-Book of Stockholm (1958), 11,289 children had been born in the city during 1957, of whom 1,339 were illegitimate, i.e. about 12 % of the total. Thus the frequency of illegitimacy in the subjects' series was not higher than one would have expected in Stockholm in 1957. The proportion of illegitimate children has remained largely unchanged during the past ten years.

In 68 of the subjects' families (48 % of the total) the mother admitted to being pregnant when she married. On the other hand, 40 of the controls' mothers (25 % of the total) had been pregnant when they married. The difference is highly significant (23 ± 5.4).

According to Quensel (1959), 25 % of all children born legitimately in Sweden between the years 1951–55, were born during the first seven months of marriage.

In other words, the frequency of marriages, contracted when the mother was already pregnant, was higher among the subjects' families than among the controls' families. It is possible that many of these marriages would have been considered, even if the mother had not been pregnant, but during the interviews, many mothers admitted that they would never have married the fathers if they had not needed help in supporting the expected child. When considering this information it should be remembered that according to the case histories from the Mariapoliklinik, many of the fathers showed no signs of chronic alcoholism at the time the mother conceived.

Summary

Ten per cent of the children of the subjects' families, were born illegitimate, but only one of the control children. Pregnancy at the time of marriage existed in 48 % of the subjects' families, but only in 25 % of the controls' families. The difference is highly significant.

Complications of Pregnancy

Apart from those cases of shortened or prolonged pregnancy which are discussed below under "Complications of labour", only a few cases of complication of pregnancy were encountered.

Such complications had occurred in five cases in the subjects' series, i.e. about 2 % of the total.

In one case (Case 23) the mother had had frequent bleedings during the last months of pregnancy. At the time of the examination the child was an imbecile (educable). In two cases (cases 29 and 78) the mother had had albuminuria, and one of them had also had oedema. The children of these mothers, at the examination, were considered to be mentally normal. One mother

(Case 31) had had pyelitis during the fourth month of pregnancy, and in this case the child was judged to be mentally insufficient. Finally, one mother, during the seventh month of pregnancy, had had nausea and fever of unknown origin. In association with these symptoms she had pains which, however, disappeared after a few days. This child was considered to be mentally insufficient.

Similar complications occurred in three of the controls, i.e. also in about 2 % of the total. One mother had had mumps during the seventh month of pregnancy, another had had "anaemia" and a third albuminuria during the last months of pregnancy. At the examination all the children were considered to be mentally normal.

Summary

Complications of pregnancy occurred in only a few cases from both series.

Labour, Feeding and Early Development

Complications of labour such as prematurity (birth weight $\leqslant 2500$ g), forceps delivery, breech delivery or post-partum asphyxia occurred in 29 of the subjects' series (17 boys and 12 girls—13 % of the total) and in 12 of the controls' (7 % of the total) (difference 6 ± 3.0). Prematurity occurred in 8 % of the subjects' series and 4 % of the controls' series, forceps delivery in 2 % of the former but not at all in the latter. For comparison, it may be stated that, according to Gyllenswärd (1946), 4.8 % of all living children, born in Stockholm hospitals between 1936–39, were premature, and forceps were used in 3.4 % of all deliveries in Stockholm hospitals during the years 1930–42.

One hundred and forty nine children in the subjects' series were breast-fed for at least three months, i.e. in 65 % of the total, while in the controls' series, there were 126 children who were breast-fed, i.e. in 78 % of the total. The difference is statistically significant (-13 ± 4.5).

Difficulties at feeding times during early life, in the form of vomiting, which was both prolonged and difficult to treat, occurred in 13 cases of the subjects' series (5 boys and 8 girls), and in two cases of the controls' series, i.e. 6 % and 1 % respectively. The difference is significant (5 ± 1.7). One of the cases in the subjects' series had been taken into hospital with a diagnosis of pyloric stenosis. This case is described below.

Case 105d: Boy, taken into hospital at the age of eight months, 25.1–8.2.55. The case history reads: "On 21.1. patient began to vomit. Continued vomiting 22.1., projectile, shortly after food. Lost weight ... Condition on admission: Development normal. Normal tone and turgor ... 26.1. Projectile vomiting. Today marked gastric peristalsis ... X-ray: Pyloric spasm with emptying greatly delayed ... 2.2. Child in excellent condition, did not vomit yesterday. Conservative treatment ... Discharged with anti-spasmodics at the mother's request.

All the other cases were largely of the following type:

Case 78: Girl, admitted to the childrens' hospital at six months of age, from 5.3. to 21.3.51. The case history reads: "Has screamed all day and night since arrival home from the maternity hospital. Was given medicine for sleep by the Child Welfare Centre and slept well for one week as a result. For the past few weeks has begun vomiting during and after certain feeds, sometimes

rather violently. Came up to the out-patient department two weeks ago and was prescribed anti-spasmodics. Vomiting stopped after treatment, but the child continued screaming."

Twenty four of the subjects (12 boys and 12 girls) were late in standing (could walk unsupported at 15 months or later), i.e. 12 % of the total, and 24 of the controls, i.e. 15 % of the total.

Thirteen of the subjects (5 boys and 8 girls) were late in talking (could not speak clearly before four years or later), i.e. 6 % of the total, and seven of the controls, i.e. 4 % of the total.

Thus the frequency of complications of labour and of late development of standing and talking was largely the same in both series. They were not appreciably different from what one would expect to find in a normal Swedish series. On the other hand, feeding difficulties were more common among subjects than among controls, while breast-feeding, for at least three months, was more common among the controls.

Summary

Complications of labour appeared in 13 % of the subjects' series and in 7 % of the controls' series, but the difference is not significant. Sixty five per cent of the subjects and 78 % of the controls were breast-fed for at least three months, a significant difference. Delayed development in walking and talking occurred in both series to about the same extent, 12 % and 15 %, and 6 % and 4 % respectively.

Previous State of Physical Health

The organic illnesses which appeared in both series are discussed below. Minor illnesses and those which disappear rapidly without sequelae are not discussed.

Central nervous diseases or symptoms occurred in 14 of the subjects (8 boys and 6 girls) and in 17 of the controls (10 boys and 7 girls), i.e. 6 % and 10 % respectively. Of these, there were nine cases of concussion (3 subjects and 6 controls), 14 cases of convulsions (6 subjects and 8 controls), four cases of meningo-encephalitis (2 subjects and 2 controls), two cases of poliomyelitis (1 subject and 1 control) and two cases of hydrocephalus (2 subjects).

The cases of poliomyelitis and meningo-encephalitis in the subjects' series are described below:

Case 58: Boy, born 1947, admitted in 1953 to the fever hospital with a diagnosis of nonparalytic poliomyelitis. Rapidly free of symptoms, uneventful recovery. On examination one month after discharge, condition normal.

Case 97b: Boy, born 1951, admitted to the fever hospital 1956 with a diagnosis of infectious mononucleosis with meningitis. On admission had severe tonsillitis and generalised adenitis. A blood count showed a leukocytosis with relative lymphocytosis. Lumbar puncture: Pandy: + +, Nonne: +, Cells: 26/c.mm.—Treated in routine way and discharged home, free of symptoms.—On examination one month after discharge, condition normal.

Case 128a: Boy, born 1947, admitted to the fever hospital 1948 with a diagnosis of purulent meningococcal meningitis. On admission had neck rigidity with pains in the joints and skin haemorrhages. Lumbar puncture: Pandy: + + +, Nonne: + + +, Cells: 23,800/c.mm (polymorphs 87 %). Culture of cerebro-spinal fluid: growth of meningococci. —On discharge mentally normal. On examination two and four weeks after discharge, condition normal.

There were two cases of hydrocephalus in the subjects' series, but none in the

controls' series. The two cases are given below:

Case 22: Boy, born 1951. Pregnancy and labour normal and at full term. Birth weight 2,800 g. Rather short time on the breast. Late in walking. First walked unsupported at 18 months of age. Still not dry or clean. Not talking. Severe motor restlessness. In 1955 investigated at a childrens' hospital with a diagnosis of internal hydrocephalus. Imbecility. Encephalography showed moderately dilated ventricles.—Institutional care advised.

Case 118: Girl, born 1949. Pregnancy and labour normal and at full term. Normal birth weight. Dull during neonatal period, and did not suck. Later whole development retarded. In 1949 and 1950 repeatedly admitted to a childrens' hospital with a diagnosis of hydrocephalus. Encephalography showed somewhat dilated lateral ventricles and markedly widened sulci in both parietal lobes. Development quotient according to Bühler-Hetzer 80.—Was in a normal class at the time of the investigation, but had difficulty in keeping up with the lessons.

There had been a number of cases of allergy in both series. Three subjects and four controls had allergic eczema, two subjects and five controls had asthmatic bronchitis, one control had allergic rhinitis and one subject had urticaria.

A boy subject had impaired hearing after repeated attacks of otitis. He also had impaired vision, but the parents had not considered it necessary to seek advice for the latter. One subject and two controls, besides, had impaired vision. One control had diabetes mellitus. Three subjects and one control had strabismus.

One of the subjects had a congenital deformity.

Case 47: Boy, born 1951. During the years 1955–58 was a patient in the surgical ward for a total period of about a year, most recently 17.2.–10.3.58. with a diagnosis of hypospadias. Operated six times in all, several times unsuccessfully because of fistula formation. Operated last 1958 with reconstruction of the urethra. Result satisfactory. According to the surgical report he adjusted himself well mentally to staying in hospital.

Three cases of congenital deformity occurred among the controls, two of congenital dislocation of the hip and one of club-foot.

Physical disease of the kind described has thus occurred in 26 subjects (18 boys and 8 girls) and 34 controls (20 boys and 14 girls), i.e. 11 % and 21 % of the totals respectively. The difference is significant (-10 ± 3.8).

Summary

Physical illness of the kind reported had occurred in 11 % of the subjects and 21 % of the controls. The difference is significant.

Out-Patient Visits

Fifty four subjects (23 boys and 31 girls—24 % of the total) and 31 controls (19 % of the total) had come up to the out-patient department one or more times with physical symptoms of different kinds.

Physical illness was confirmed in 13 of the subjects and 22 of the controls, i.e. in 6 % and 13 % of the series respectively. The difference is not statistically significant (-7 ± 3.1).

The remaining 41 subjects (16 boys and 25 girls) and nine controls, i.e. 18 % and 6 % respectively, had come up to hospital complaining of physical symptoms for which no definite underlying organic

normality could be found. The difference is highly significant (12 ± 3.1).

The majority of these latter cases had symptoms such as headache, atypical abdominal pain, palpitations, tiredness and general debility. In some cases the symptoms were more diffuse and difficult to diagnose. The following cases from the subjects' series serve as examples of the former type:

Case 17b: Girl, born 1951, attended the medical out-patient department of a childrens' hospital in 1958 complaining of pain in the abdomen. Felt very tired, and sometimes, recently, could not even get up in the mornings. On examination nothing abnormal found. Prescribed anti-spasmodics.—On one occasion driven to hospital by ambulance because of abdominal pain. On arrival was found to be quite normal. Same treatment prescribed as before.

Case 33a: Girl, born 1947, attended medical and surgical outpatient departments repeatedly between 1956 and 1957 because of diffuse abdominal pain, nausea and headache. Often complained of tiredness. The symptoms were most pronounced in the evenings. Sometimes lay down and cried, not sleeping until midnight. Condition normal at each visit. Prescribed anti-spasmodics.

Case 36a: Boy, born 1947, attended medical out-patient department of a childrens' hospital in 1957 complaining of general tiredness, irritability and sleeping difficulties. Had had similar difficulties for short periods earlier, but has become worse. Condition quite normal. Prescribed anti-spasmodics and tonics.

Case 38b: Boy, born 1953, attended medical out-patient department of a childrens' hospital in 1956. Had been afraid to sit on the pot for about six months, "wets and dirties himself immediately after he has been dressed. Wakes every night and wishes to creep into the mother's bed.—None of the relatives have experienced anything similar."—Condition quite normal. Light diet prescribed.

These case records should be sufficient to delineate the symptom pattern. All the cases are similar except that in one the symptoms appear in the abdomen, one in the heart and one in the head. Over and over again, the patient returned to the out-patient department, or the general practitioner, but the treatment, usually medical, which was prescribed, did not seem to reduce the symptoms to any appreciable degree.

In other cases, as already mentioned, a more diffuse symptom-picture appeared, which in the beginning can seem alarming and sometimes leads to prolonged and, for the child, difficult examinations and investigations without anything objective being found. The following examples from the subjects' series can be quoted.

Case 55: Girl, born 1949, attended medical out-patient department of a childrens' hospital in 1958, complaining of pain over the precordium together with palpitations, sometimes in association with nausea and vomiting. At the investigation which, besides a physical examination, included electrocardiography with phonocardiographic recording, nothing abnormal was found. Discharged with sedatives after repeated visits as an outpatient.

Case 62: Boy, born 1946, attended medical out-patient department of a childrens' hospital in 1958 because of general tiredness and headache. In addition had recently had peculiar attacks, in which he stared straight out into space and "feel that I am going to faint". On a number of occasions, irregular, asymmetrical twitches in the arms and legs. Condition quite normal. Electroencephalography: no specific epileptogenic activity. Discharged after repeated visits to the out-patient department with prescriptions for sedatives.

Case 81b: Girl, born 1948, came to the out-patient department of a childrens' hospital complaining of pain on defecation. Has

always had a tendency to constipation. Recently increasing loss of appetite. Condition: small, thin and pale, "below normal from all points of view". Colon full of faecal masses, some of them hardened. Manual evacuation. Continued treatment and checks arranged, but the patient did not return.

Case 114a: Girl, born 1947, attended the medical out-patient department of a childrens' hospital in 1956, complaining of abdominal pain and regurgitation of food remains between meals. Tolerated all kinds of food. Previously operated for the same complaint without finding anything noteworthy in the abdominal cavity. The appendix was normal macro- and microscopically. Also visited another hospital in the interval, but nothing abnormal was found on examination. Anti-spasmodics were prescribed without effect. Condition remains normal. X-rays of the stomach and oesophagus were normal. Continued checks arranged, but the patient did not return.

Case 140a: Girl, born 1950, attended general practitioner in 1957 for abdominal pain. Was always running to the toilet, but could not sit down, because she thought that "it hurts in my bottom". Sometimes she would stand staring straight out into space and appeared to be miles away. Sometimes refused food. Condition normal on examination. Sedatives prescribed and told to come back, but did not do so.

It should be pointed out, that in not one of these 41 subjects, who attended the hospital with symptoms for which no definite explanation could be found, was the home situation mentioned in the case history. In those cases where the investigation was prolonged, or where the psychological basis of the symptoms was being suspected, the parents have usually broken contact with the hospital or general practitioner, in spite of the childrens' symptoms persisting unaltered. In several cases the parents have gone from one hospital to another for advice without stating that they had previously been to other hospitals (see Case 114a above).

According to information from the mothers, the fathers of all the abovementioned subjects were alcoholics at the time of the investigation of the child.

Summary

Twenty four per cent of the subjects and 19 % of the controls attended the out-patient department at least once with physical symptoms. No organic basis for these symptoms could be found in 18 % of the subjects and 6 % of the controls (difference 12 ± 3.1).

Admittance to Hospital

Seventy eight subjects (44 boys and 34 girls) and 44 controls (28 boys and 16 girls), i.e. 34 % and 27 % respectively, had been in hospital. Only one of the 78 subjects (Case 114a) has also been mentioned in the section on "Out-patient visits".

Unmistakable physical illness had been seen in 55 subjects (33 boys and 22 girls) and in 37 controls (25 boys and 12 girls). The remainder, 23 subjects (11 boys and 12 girls), i.e. 10 % of the total, and seven controls (3 boys and 4 girls), i.e. 4 % of the total, had been in-patients in hospital without any definite organic cause for the illness being found. The difference is almost significant (6 ± 2.4).

The 23 subjects who were kept in hospital without a definite aetiology are set out below:

Case 2b: Boy, born 1950, who was admitted to a childrens' hospital at the age of two months with a diagnosis of vomiting, acute dyspepsia? Stay in hospital 18 days. Had been vomiting for about 1 ½ months, slowly increasing, now after every feed.

First vomited a large quantity and then smaller quantities the whole time until the next feed. Anti-spasmodics given without effect. Condition on admission: Rather thin, and flabby, but not dehydrated. No visible contraction of the stomach.—During stay in hospital, rapid improvement, and on discharge, only very slight vomiting at feeds. Advice given on feeding, but no other steps taken.

Case 14a: Girl, born 1945, in 1954 was patient in a childrens' hospital with a diagnosis of post-infective myocarditis. Hospital stay 28 days. Coughed for some weeks especially at night, but otherwise seemed quite well. No dyspnoea or "any kind of subjective heart symptoms". Had been to general practitioner for investigation of the cough. After an electrocardiogram had been taken, the result showed that "the heart did not function as it should", and so was sent up to hospital.—Condition on admission: "A thin girl with good colour. No cyanosis or dyspnoea. Heart, no enlargement. Systolic thrill. In the 3rd–4th inter-space a short systolic murmur was heard. Rhythm regular but fast. Liver and spleen not palpable." Ecg: myocarditis.—Four days after arrival, it was noted that the patient had been well and free of symptoms all the time. "The heart rate is clearly very labile and affected by mental stimuli."—On discharge: "Feels very well, no subjective or objective heart symptoms." Continued to come for outpatient checks for "an inconstant murmur which gradually disappeared." (4.6.58.)—On re-examination of the X-ray and Ecg tracings (Dr. Tage Möller, K.L.B.) it was observed: "While in hospital the diagnosis of post-infective myocarditis was made on the basis of the Ecg changes which existed. In a number of the electrocardiograms an almost iso-electric TII and a negative TIII have been seen, which were interpreted as signs of myocardial damage. This change has been intermittent in nature, and the other Ecg recordings have been normal. After 8.12.54., the Ecg are quite normal.—The changes in the T-wave noted as pathologic. in 1954 were almost certainly not signs of involvement of the myocardium. Other signs of myocarditis such as conduction disturbances, are missing."

Case 28: Girl, born 1946, in 1957 was an in-patient in a country hospital with a diagnosis of: Acute abdomen under observation. Stay in hospital, four days. Previously healthy. Came in the evening and "had just had abdominal pain, in the region of the umbilicus, but on arrival felt rather well again".—On examination, no abnormality found. After being observed for four days without recurrence of symptoms, was discharged without anything further being done.

Case 32a: Girl, born 1947, admitted to a childrens' hospital in 1954 with a diagnosis of "Case for observation + oxyuria". Stay in hospital, 39 days. Previously well but wet the bed. Had been having "strange attacks" for the past six months. In October 1953, she suddenly fell down while standing. She appeared to be "far away". No convulsions. Got up after a moment and was then quite normal again. More recently had had a similar attack. On admission to hospital, physical condition normal. EEG no essential abnormalities.—During stay in hospital fell in paddling pond and got wet. Next day "was completely dumb". Lay on the bed, without moving, refusing to answer questions, would not speak with other patients. "Unchanged the whole day until evening, when she began to talk and play again as usual. During the EEG examination, the same thing happened again. Her previous attacks may well be considered as psychogenic."—Discharged home without further psychological investigation or suggestions for treatment.

Case 50: Girl, born 1946, was patient in a childrens' hospital in 1953, with a diagnosis of mesenteric lymphadenitis. Stay in hospital six days. Previously healthy. For six days had had nausea, vomiting and abdominal pain. Operation: a macroscopically normal appendix. A number of swollen injected glands of hazelnut size near the ileo-caecal junction.—Discharged symptom-free.

Case 57a: Boy, born 1949, admitted to a childrens' hospital in 1957 with a diagnosis of acute mesenteric lymphadenitis. Stay in

hospital, seven days. Previously healthy. Had had abdominal pain in the morning for a month, now intermittent. Nausea constantly, but no vomiting. Operation: appendix macroscopically healthy. Profuse, bean-size, acutely inflamed mesenteric glands.—Discharged symptom-free.

Case 76: Boy, born 1950, in-patient in a childrens' hospital in 1957 with a diagnosis of cephalalgia. Stay in hospital, 14 days. Previously well. Since summer 1955 headache attacks. Sometimes vomits at the same time.—Examination on admission showed no abnormality. EEG normal. Encephalography: Normal condition. During stay in hospital, quite symptom-free. Psychiatric consultation (the author): "Gives the impression of having a neurosis. Referred to child-guidance clinic."—Never presented himself there however.

Case 97a: Girl, born 1945, admitted to a childrens' hospital in 1951 with a diagnosis of C-hypovitaminosis. Stay in hospital, 15 days. Previously healthy. Came in with abdominal pain at meal-times, together with poor appetite. Appeared tired and peevish. On admission had many bruises, mainly on the lower leg, but also on the trunk. There was a small area of petechiae on the chest as well as a number on the arms. Examination, otherwise normal. Hb.: 13.8 g.%. R.B.C.: 4,500,000/c.mm. Thrombocytes: 280,000/c.mm. Bleeding time, 2 min. 10 sec. Coagulation time 3 min. 25 sec. Göthlin's test, negative. Test meal—presence of free acid. Determination of ascorbic acid in the urine: 3 mg.%.—On discharge is noted: "Since it is not possible to find vitamin C in the urine, and since the petechiae have diminished since the patient was put on massive doses of ascorbic acid, a deficiency of vitamin C must have existed."—According to the mother when interviewed seven years later, the father had often hit the girl so that she developed bruises. The mother considered it quite possible that the bruises the girl had in hospital were caused by blows from the father.

Case 110a: Girl, born 1949, in-patient in a childrens' hospital in 1955 with a diagnosis of mesenteric lymphadenitis. Stay in hospital, five days. Previously healthy. For the last six months had had periodic diffuse abdominal pain.—Operation: appendix macroscopically normal. A number of inflamed glands the size of a pea in the mesentery of the small intestine. Discharged, symptom-free.

Case 114a: Girl, born 1947, in-patient in a childrens' hospital in 1955 with a diagnosis of mesenteric lymphadenitis. The case described on p. 42.

Case 122a: Boy, born 1946, was in a country hospital in 1950 with a diagnosis of acute mesenteric lymphadenitis. Stay in hospital, six days. Previously, often diffuse abdominal pain. The night before admission, pain over the whole abdomen. Operation: appendix normal. Many brown-bean-sized glands in the mesentery. Discharged symptom-free.

Case 135: Girl, born 1949, in-patient in a childrens' hospital with a diagnosis of mesenteric lymphadenitis. Stay in hospital, five days. Previously healthy. Past few days, severe pains in the abdomen, "to-day really bad stomach-ache".—Operation: appendix normal. The mesentery was full of glands up to the size of dessert-almonds.—Discharged, symptom-free.

From the above, it can be seen that mental factors must have played a decisive part in the development of symptoms in many of the cases. In other cases, there was greater uncertainty concerning the aetiology. The latter concerns those cases with a diagnosis of mesenteric lymphadenitis. That these cases were included, in spite of this uncertainty, is explained by the fact that at interview they all stated that their symptoms had remained unchanged after the operation, although on discharge from hospital they were free of symptoms. In these cases, even if a certain organic basis cannot be precluded, mental factors may well have contributed to the symptoms being presented in

such a way that the patients came to operation with a suspected appendicitis. Ekström & Nylander (1959) were able to establish that in children after appendicectomy, in whom the appendix had been found to be healthy, the frequency of neurosis was about nine times as high as among those who had a pathological appendix. It can be mentioned that of the seven subjects operated for suspected appendicitis, acute appendicitis was confirmed in only one case.

The other eleven subjects lying in hospital had largely had feeding difficulties. Thus seven of them lay in hospital during the first year of life. They had vomited at meal-times during infancy. All became quite symptom-free, even including one case with a diagnosis of pyloric stenosis (see p. 38).

The diagnosis in one case (a boy) was sleep disorder, in another (a girl) constipation and in a third (a girl) sleep disorder plus rickets. In every case, freedom from symptoms soon after they came to hospital. Finally, a fourth case had been in hospital largely on account of the home conditions. because the mother, at the time, was not capable of looking after the child.

Of the seven controls who were in hospital without demonstrable organic cause of the symptoms, four had been admitted for suspected appendicitis. Three of these had been operated. In every case the appendix was healthy, but enlarged swollen glands were visible in the mesentery in two of the cases. One case was admitted to hospital for some days with vomiting, which was interpreted as ketotic, one with constipation and symptoms of enuresis and finally, one case with disorder of sleep. All the controls had been in hospital less than two weeks.

If the subjects and controls are compared with each other it can be seen that the subjects had more varied and dramatic symptoms than the controls.

In not one of the subjects' case-histories was a note made about the father's alcoholism or about any other unusual home conditions, in spite of the fact that the father, in all of these cases, was already an alcoholic at the time. The father was simply described as "healthy". If the doctor concerned, who looked after the patient, had had full insight into the true home-conditions not only would expensive time in hospital have been saved, but also the children could have been helped in a more adequate way. Without knowledge of the home conditions, the examining doctor in every case had been compelled to carry out comprehensive and time-consuming investigations, and sometimes also surgical interference for which there were not always positive indications. With a proper history the doctor's treatment would certainly have been different in the majority of cases.

Summary

Thirty four per cent of the subjects and 27 % of the controls had been in hospital. Ten per cent of all the subjects and 4 % of all the controls had been in-patients in hospital without organic cause for the symptoms being found. This difference is almost significant. The subjects' case-histories contain no information about alcoholism in the father, or of unusual home-conditions. Therefore this has not been taken into consideration in the diag-

nosis and treatment of the childrens' symptoms.

Visits to the Child-Guidance Clinic

Thirteen subjects (7 boys and 6 girls—6 % of the total) and eight controls (4 boys and 4 girls—5 % of the total) had consulted a child-guidance clinic. It can be seen that the frequency of consultation was largely the same in both series.

The subjects' case-histories are set out in brief below.

Case 4: Girl, born 1947, came up to the child-guidance clinic in 1954 because of retarded development and stuttering. She was shortly due to begin school. Contact with the child-guidance clinic was short. I.Q. on the Terman-Merrill scale 73. It was advised that she should be put in a special class in a normal school or in a special school. She was later put in a special class (I.Q. 70–85), where she could keep up with the others quite well. She always had pronounced nervous symptoms, and at the time of examination was still mentally insufficient. The child-guidance clinic was not aware that the father was an alcoholic.

Case 15: Girl, born 1947, came up to the child-guidance clinic many times between the years 1952 and 1954 because she was difficult to manage and had difficulties with companions. Wet the bed regularly every night. From the examinations it appeared that she was "extremely tense" and had "a tendency towards panic and anxiety". Her play in the sand-pit was noted as being "rigid". I.Q. on the Terman-Merrill scale 90. In the case-history it was pointed out that "she is in very great need of help". The possibility of putting her in a treatment-home was discussed, but the parents refused, breaking off contact with the child-guidance clinic and not returning, in spite of the fact that the symptoms remained largely unchanged up to the time of this investigation. Her mental state was noted by the author at the examination as being insufficient. The child-guidance clinic was unaware that the father was an alcoholic.

Case 22: See p. 40.

Case 23: Boy, born 1953, came up to the child-guidance clinic in 1958 on one single occasion, because of retarded speech development. In addition, nervous symptoms in the form of motor restlessness and difficulties with companions. Masturbated excessively and had enuresis and encopresis.—Analysis and treatment of this case is in progress.—The child-guidance clinic was aware that the father was an alcoholic.

Case 45: Boy, born 1952, came up to the child-guidance clinic in 1957 because of retarded speech development. Examination showed great difficulties in articulation, but mentally he was quite normal. Development quotient according to Bühler-Hetzer 103.—Referred for speech therapy which is being continued. The child-guidance clinic was aware that the father was an alcoholic.

Case 81a: Boy, born 1946, was admitted to a child psychiatric ward in 1953 with a diagnosis of neurosis. Came up to the child-guidance clinic from 1951–58 for encopresis. Examination showed a pronounced anxiety state. While in hospital the encopresis rapidly disappeared, but "it had a tendency to return after a week-end at home". In the case-history it was further noted that "the father had always been very much a family man, never amused himself apart from his family and does not drink". In the child-guidance clinic's case-history it was noted that "the father was desirous of getting help, made a rather good impression and seemed to be very fond of the children". However, the father often rang cancelling the appointment at the child-guidance clinic and finally would not come himself for discussions. In the end, the mother also failed to keep pre-arranged appointments, in spite of the fact that the boy's symptoms remained. They still exist, largely unchanged. On examination by the author, he was noted as being mentally insufficient. The father was not known to be an alcoholic at the child-guidance clinic.

Case 81b: Girl, born 1948, came up to the

child-guidance clinic on one single occasion in 1954 because of retarded development and distaste for food. Often had hysterical outbursts. While the examination was being made it was noted that she was "childish in her play ... does not give the impression of being neurotic". I.Q. on the Terman-Merrill scale 103. The parents broke off the analysis although they were repeatedly contacted. The symptoms have remained, largely unchanged. On examination by the author, however, she was not considered to be mentally insufficient. The child-guidance clinic was not aware that the father was an alcoholic.

Case 84b: Boy, born 1949, was reported to the child-guidance clinic in 1958 because of anxiety, difficulty with companions and enuresis, but who at the time of the investigation had not yet been there. On examination by the author was noted as being mentally insufficient.

Case 117: Girl, born 1948, came up to the child-guidance clinic during the years 1956–58 because of anxiety, night terrors and "peculiar attacks". The symptoms have been in existence since the age of three, showing a tendency to increase. Occasional outbursts when she appeared "completely disorientated, opening doors for invisible guests, etc.". Complained of palpitations and abdominal pain, was always tired, would rather lie down, even during the day-time. Visited the heart clinic for palpitations: objectively nothing abnormal. At the child-guidance clinic she gave an impression of being very ill and a note was made in the case-history of "certain psychotic features". The treatment at the child-guidance clinic ended unsuccessfully. On examination by the author she was judged mentally insufficient. The child-guidance clinic was aware of the father's alcoholism.

Case 119a: Boy, born 1946, visited the child-guidance clinic between 1952 and 1955 because of emotional outbursts and difficulties with companions. Frequent headaches. In 1955 was examined at the neurological outpatient department for these: neurologically normal. On examination at the child-guidance clinic was unable to concentrate but otherwise not abnormal. I.Q. on the Terman-Merrill scale 134. The father was reported as having a good relationship with the boy, who "adores his father".—The mother broke off contact with the clinic in June 1955, but resumed it again in January 1956 and mentioned then, for the first time, that the father was an alcoholic, being aggressive and disturbing in the home. At that time she wished for a divorce.—On examination by the author, the boy was considered to be mentally insufficient.

Case 122b: Boy, born 1948, sought the advice of the child-guidance clinic in the years 1955–56 because of pilfering, difficulties both with companions and adaptation to schoollife. Periodically stubborn and self-willed. The examination showed that it was difficult to make contact with him, that he was suspicious, and over-anxious. I.Q. on the Terman-Merrill scale 98. EEG normal.—The final note in the case-history reads: "I notice that the mother is very reluctant to maintain contact with us. Is discharged." The symptoms remain, unchanged, and at the time of the present investigation, the author judged the boy as being mentally insufficient. The father's alcoholism was unknown by the child-guidance clinic.

Case 123b: Girl, born 1948, visited a child psychiatrist privately in 1958 for depression, difficulty in sleeping and hysterical outbursts. Severe headaches daily. Examination and treatment in progress. On examination by the author was noted as mentally insufficient. The child psychiatrist concerned was aware of the father's alcoholism.

Case 131a: Girl, born 1946, was under the care of the child-guidance clinic from the years 1950–52 for difficulties with companions, refusal to eat and enuresis. Attacks of panic. Examination showed "pronounced anxiety symptoms and signs of depression". Development quotient according to Bühler-Hetzer 96.—Contact broken off by the parents. On examination by the author noted as mentally normal. The child-guidance clinic was not aware of the father's alcoholism.

It can be seen from the above, that all the subjects, who were examined by the child psychiatrists, were in great need of examination and treatment. The presenting mental symptoms had usually been in existence for a long time, and in the majority of cases seriously upset the child's adaptation. The parents most often showed very little inclination to co-operate in getting the child well. In six cases the father's alcoholism had been concealed, in spite of the fact that both mother and child had come to examination and discussion many times, and in every case the father was already an alcoholic at the time. In several cases the parents broke off examination and treatment before the doctor considered them to be complete and while the child's symptoms remained unchanged in extent and severity. On the whole, the parents have been grateful and accepted the offer of examination and treatment so long as these concerned only the child itself. As soon as the examination encroached on those causes and problems which lay behind the child's symptoms, the treatment was broken off. In eleven of the 13 cases examined at K.L.B. the mental condition of the child has been considered insufficient, despite the fact that in a number of cases some years had elapsed since the last visit to the child-guidance clinic.

Summary

In about 6 % of the subjects (13 cases) and in about 5 % of the controls (8 cases) psychiatric help had been sought for the nervous symptoms of the children. In the majority of the subjects the treatment was not completed, but was broken off by the parents, in spite of the fact that the examinations were performed by trained child psychiatrists. In six of these cases the respective institutions were not aware of the father's alcoholism.

Conditions in School

The number of subjects of school age, i.e. had reached the age of seven during the year 1957, was 141 (63 boys and 78 girls). One of these, a boy, had had his schooling deferred because of immaturity (examined with a school-maturity test), but all the others went to school.

The majority of these (134 cases, 57 boys and 77 girls) had been placed in a normal class, while six (5 boys and 1 girl), were in special classes. Of the latter, three (2 boys and 1 girl, i.e. 2 % of the total) were in a special class for retarded children (I.Q. between 70 and 85) and two (both boys, i.e. 1 % of the total) were in so-called "reading class" (intended for children with normal I.Q. but with reading and writing difficulties).

On the 15th of September 1958 in the elementary schools of the City of Stockholm, 3 % of the children were in the special class for retarded children, 2 % in the "reading class" Thus, the placing of the subjects in school did not differ, to any degree, from the average for the City of Stockholm in the year 1958. In any case, the frequency of subjects in special classes was not higher than among Stockholm children in general.

As previously stated, the controls had been selected partly on the principle that every subject of school age should have a class-mate as control. Placing in school among the controls' series was thus similar to that of the subjects.

In order that each subject should have a

TABLE 6. *Comparison between school reports of subjects and controls.*

Report total, points	Subjects			Controls		
	♂	♀	♂+♀	♂	♀	♂+♀
3–4	4	1	5	2	0	2
5–6	10	13	23	10	15	25
7–8	10	11	21	12	10	22
9–10	5	10	15	7	11	18
11–12	4	1	5	2	2	4
13–14	2	2	4	1	1	2
15–16	1	2	3	2	0	2
17–18	0	0	0	1	0	1
19–20	1	0	1	0	1	1

control with approximately the same intellectual ability as the subject himself, an effort has been made to choose controls with similar report totals as the subjects. In Table 6 the report totals have been compared (1 point corresponds to pass, 1.5 to credit, 2 to good, 2.5 to very good and 3 to excellent). When adding up the total number of points, individual subjects were not considered. The great difference between the lowest and the highest numbers of points is explained by the fact that in the lower classes, the number of subjects is less than in the higher classes. In the majority of cases the low totals are those of the children in the lower classes. The children in the bottom class are not included in this table as school reports are not distributed until the second year.

It can be seen from the table that the reports are of similar standard in both series. The average difference between the report totals of subjects and controls was only 0.07 of a unit, in favour of the controls.

Summary

Of the 141 subjects who were of school age, 134 were in a normal class, three were in a special class for retarded children, and two in a "reading class". One had had his schooling deferred because of general immaturity. The average report totals were largely the same both for the subjects and the controls. The latter had also been chosen from the point of view of equality in school achievements according to the schools' points system.

Health Supervision by the Child-Welfare Centre

Swedish children receive free medical advice at the Municipal child-welfare centre during the first years of life. They usually attend four times in the first year and somewhat less frequently later. Most mothers take advantage of this service. In 1948, 77.6 % of all new-born children in the City of Stockholm were examined at least once, in 1953 the figure was 87.2 % and in 1958, 92.8 %. The corresponding figures in the subjects' series were considerably lower.

For practical reasons only children on the City of Stockholm's lists were included. A search was made for the case-histories of all the subjects born in 1951 or later, a total of 82 cases (47 boys and 35 girls) in the records departments of the

child-welfare centres. Only 45 case-histories were found (26 boys and 19 girls), i.e. 55 % of the total. In only eleven of these (4 boys and 7 girls) had the father's alcoholism been either revealed or suspected.

Children born in 1950 or earlier were studied in a similar way. Since case-histories at a number of child-welfare centres are destroyed after the child is ten years old, in some places even earlier, information could only be obtained about a further 38 cases (16 boys and 22 girls), born in 1949 and 1950. The records of children born in 1948 or earlier had been destroyed by all the child-welfare centres. Of these 38 cases only 16 (7 boys and 9 girls) had visited the child-welfare centre, i.e. 42 % of the total. In six of these latter cases, the father's alcoholism was known or suspected.

Of the total of 120 cases (63 boys and 57 girls) under discussion, only 61 (33 boys and 28 girls—51 % of the total) were seen at the child-welfare centre.

Summary

Only about 50 % of the subjects registered in the City of Stockholm were seen at the child-welfare centres. In the majority of those cases attending, neither the doctors nor the nurses were aware of the fathers' alcoholism.

Contact with the Children's Care Committee

In 18 families, 13 % of the total, the Children's Care Committee had received a report that the father was alcoholic to such an extent that the children ran the risk of being injured (cases 19, 21, 22, 23, 24, 30, 38, 56, 66, 78, 84, 87, 88, 91, 98, 113, 115, and 124). The initiative in reporting had been taken in the majority of cases by the Temperance Board (7 cases) and the mother (4 cases). In the remaining cases social workers (3 cases), the child-welfare centre, a general practitioner and a neighbour had reported the family, and in one case the report was anonymous. As a result of these reports the Children's Care Committee had taken action in 17 cases, while in one (case 38) no action was taken.

The most common course of action, supervision, was taken in eleven cases (cases 21, 22, 23, 30, 66, 84, 87, 91, 98, 113 and 124). At the time of the investigation the supervision had been discontinued in six of the eleven cases (cases 21, 23, 30, 84, 91 and 98). However, in two cases this was in spite of the fact that indicated that the home situation had not changed since the time of the report. These two cases are described below.

Case 23: According to the report of the Children's Care Committee: The mother reported the father because he appeared permanently drunk and at the same time ill-treated the child ... placed under supervision, which was discontinued "since the conditions for a long time now seem to have stabilised themselves, and the child's father has not lived at home since Christmas 1956". (Written in January 1957.) ... according to the mother the home conditions at the time of the examination were unchanged. The father came home regularly drunk, and was both aggressive and brutal towards the mother and the child....The child, an only child is mentally backward.

Case 84: According to the report of the Children's Care Committee: The mother reported the father since he was constantly drunk. After investigation, supervision. The case was concluded in September 1957 since "the father made serious attempts to come

to terms with his alcoholism".—According to the mother at interview: Unchanged up to the first of January 1958. Still aggressive, brutal, and restless at night.—At home, three children aged 14, 10 and 9, all severely neurotic.

In five cases the children had been taken away from the home, two of them being placed in a foster home (Cases 78 and 88) and three in a children's home (Cases 19, 23 and 115). The reason in all these cases was that the mother was sick or having a baby, and was therefore unable to look after the children at that time. Later, all these children returned to their own homes.

One child, mentally backward (Case 22) was placed in a home for the care of imbeciles through the intervention of the Children's Care Committee.

The case not requiring action on the part of the Children's Care Committee was as follows:

Case 56: According to the report of the Children's Care Committee: Reported by the Temperance Board in April 1957. The father was a dangerous alcoholic. It appeared from the investigation of the Children's Care Committee that "the father pulled himself together and behaved perfectly after he made up his mind to stop drinking". "The daughter does not appear to have been much affected by the earlier unsettled home conditions."—On examination by the author no abnormal mental symptoms could be found, but according to the mother, the father continued to drink, although he was not as aggressive or violent at home as he had previously been.

From the above, it appears that the Children's Care Committee only knew a few of the 141 subjects' families who were severely disturbed by the father's alcoholism. In a previous section it was stated that the father's alcoholism was known to the Temperance Board in 97 cases. In other words, the Temperance Board only exceptionally considered that the father's alcoholism was so severe as to warrant measures being taken by the Children's Care Committee. In addition it may be mentioned that the doctors at the Mariapoliklinik noted drunkenness in 75 of the subjects' fathers as being severely disturbing, and that 22 subjects' fathers were incapable of supporting their families.

Since the first of May 1958 there has been a special section of the Children's Care Committee in the City of Stockholm, which includes among its functions that of dealing with cases which are reported by the Temperance Board. The law on the care of alcoholics directs that: "There should be mutual co-operation between such authorities and the Public Assistance Committees, Children's Care Committees etc." In the City of Stockholm in 1958, 9,051 cases of alcoholism were reported to the Temperance Board. Between 1.5.58. and 30.4.59., the above mentioned section of the Children's Care Committee only received 130 reports from the Temperance Board.

None of the controls has been reported to the Children's Care Committee.

Summary

The father's alcoholism had come to the notice of the Children's Care Committee in only 13 % of the subjects' families, i.e. 18 families. In one case the committee had removed the child from home permanently, while in the other cases the question was one of temporary supervision (11 cases), or placing in a foster-home (2 cases), or in a children's home (3 cases).

Physical Condition

At the time of examination, the general state of health was good on the whole in both series.

The body-height in every case was within the normal limits according to Broman, Dahlberg & Lichtenstein (1940). (The limits of variation estimated so that only 1/2 % exceed or fall below the stated maximum and minimum values.)

The body-weight, considered in relation to the body-height, was within normal limits in the whole series, except for three subjects and one control. Two of the subjects were under-weight, Cases 107b and 140a, described here:

Case 107b: Girl, born 1952, who at the time of the examination was in the fever hospital with scarlet fever. Both the father and the mother were severe alcoholics, the mother, in addition, being a drug addict (see p. 31). The child was often left without supervision and care. As far as is known, previously well, both physically and mentally. On examination: Thin, but otherwise normal. Height: 115 cm. Weight: 14.1 kg. Mentally normal.

Case 140a: Girl, born 1950. Full-term delivery. Birth-weight 2900 g. Infancy and rearing normal. Early motor and mental development normal. For several years had complained of diffuse abdominal pain, and periodically refused food. Very sensitive. Nocturnal enuresis continues. Had not previously visited a doctor.—On examination: Thin and pale, otherwise normal. Height: 139 cm. Weight: 21 kg. Mentally: anxiety neurosis.

One subject weighed 18 kg. more than the average for his height.

Case 109: Boy, born 1947, previously well. Always had a good appetite, "eats continuously both during and between meals, impossible to restrain". Worse when he is nervous.—On examination: Fat, otherwise normal. Height: 154 cm. Weight: 60 kg. Mentally: anxiety neurosis.

On physical examination, there were pathological findings in 19 subjects (9 boys and 10 girls—8 % of the total) and in 13 controls (6 boys and 7 girls—also 8 % of the total).

One case of craniotabes-like softness in the skull bones was found among the subjects.

Case 12a: Boy, born 1953. Born one month prematurely. Birthweight 2900 g. Infancy normal. Breast-fed three months. Was late in talking, first walking without support at the age of 17 months. Frequent upper respiratory tract infections. In 1956 was in a children's hospital with asthmatic bronchitis and acute brochopneumonia. Always oversensitive and uncertain of himself. Stutter. —On examination: Pale, snuffly and with prononunced softness of the skull bones. No skeletal changes palpable elsewhere. Mentally: anxiety neurosis.—Referred for continued investigation but did not attend.

Strabismus occurred in eight cases (2 boys and 6 girls), of whom six had alternating strabismus with full vision in both eyes. In two cases vision was diminished in one eye (0.1 in both cases). One boy had a deformed penis (Case 47, described on p. 40). Neurological symptoms were found in four cases. One of these (Case 22, described as hydrocephalic) had athetotic-like movements of the head together with pronounced protrusion of the upper jaw. Another (Case 118, described as hydrocephalic) had a unilateral oculomotor paresis. A third (Case 129a, described as having had meningitis) had a neurogenic hearing impairment. Finally, a six-year-old girl had bilateral loss of ankle-jerks

of unknown origin. She was referred for continued examination, but did not appear when she was supposed to. One boy had had a recent fracture of the radius which was reduced and put in plaster. In two case occurred physical symptoms which were interpreted as being secondary to mental disturbances. In one case a thick connective-tissue band was felt inside the mouth. This had developed as a result of the child's chewing the inside of his cheek for several years (Case 136a). In another case large infiltrating sucking-marks were present on the lower lip (Case 140*b*).

Strabismus was found in seven controls (3 boys and 4 girls), of whom one had impaired vision in one eye, while the others had full bilateral vision. One boy was short-sighted and wore glasses. Neurological symptoms appeared in two cases. One girl had unilateral peroneus paresis of unknown origin, while the other, also a girl, had unilateral optic atrophy. Acute allergic eczema appeared in one case. One boy had club-foot, which had previously been operated, and finally one boy had a chronic blepharitis.

When the material was chosen the upper age-limit was set at 12 years of age, in order to avoid puberty. In a number of cases in both series, however, physical puberty had already begun. For practical purposes judgement was limited to girls. Two of the 50 girl-subjects, between 10 and 12 years of age began menstruating soon after their twelfth birthdays (Cases 63 and 70d), while this occurred in three of the 31 girl-controls, who belonged to the same age-group. In the 7–9 year old group, none had begun menstruating. Physical puberty changes (early breast development), occurred in ten girl-subjects and three girl-controls, all between ten and 12 years of age.

In many cases, the state of the teeth was very bad, with the majority of the teeth severely affected by caries, even in children who had been at school for several years, and yet the child had not been to a dentist. Thus, one seven-year-old boy (Case 129) had only dirty, infected roots left in both upper and lower jaws.

No attempt has been made to estimate the frequency or extent of the caries. On the other hand, notice was taken of whether the teeth were healthy or affected by caries and whether they had been filled or not. Table 7 shows the condition of the teeth in both series. This indicates that the girl-controls more frequently had carious, filled teeth than the girl-subjects (difference 19 ± 7.0), while the frequency of carious, filled teeth among the boys was largely the same in both series. The frequency of unfilled teeth is higher among the subjects than among the controls. Thirty-nine per cent of the subjects have unfilled teeth as against only 21 % of the controls. The difference is highly significant (18 ± 4.5).

Summary

The general state of health was good in the majority of cases in both series. Two of the subjects were under-weight, but all the controls had weights exceeding the minimum value for their age. On examination, pathological changes were found in 8 % of both subjects and controls. These findings are described. Two of the girl-subjects and three of the girl-controls had begun menstruating. Condition of the teeth was assessed. The frequency of carious, unfilled teeth was 39 % among the

TABLE 7. *Condition of the teeth in the subjects (S) and controls (C).*

Condition of teeth	Sex	Subjects (S) Total no.	%	Controls (C) Total no.	%	Difference S–C
Perfectly normal	♂	113	10	83	19	0
	♀	116	13	80	13	0
	♂ + ♀	229	11	163	16	0
Carious teeth with fillings	♂	113	52	83	60	0
	♀	116	47	80	66	—**
	♂ + ♀	229	50	163	63	—**
Carious teeth without fillings	♂	113	38	83	20	**
	♀	116	40	80	21	**
	♂ + ♀	229	39	163	21	***

subjects and 21 % among the controls. The difference is highly significant.

Mental Condition

In this section an account is given of the presenting symptoms, then of the mental condition when seen at K.L.B., and finally, where school children are concerned, of the mental condition as judged by the child's teacher. At the end, the various results are compared with one another.

Presenting symptoms

The questionnaire, used when the mothers were interviewed, was concerned with a list of symptoms. The questions, as a rule, were formulated so that they could be answered with "yes" or "no". Where a positive reply was obtained, the picture was later amplified by a request for more detailed information. Questions which required a detailed answer, such as the child's interests, personality, etc., have been avoided.

However, even though the parent interviewed answered in the affirmative about a symptom, this was not necessarily recorded. In addition, it was necessary that the symptom in question should have had a certain intensity and duration. Thus, the symptom should have constituted a problem for the child or the members of the family, and have been in existence for at least three months. By this means, mental symptoms which were mild or difficult to assess, were avoided. By studying the questionnaire (See appendix), it can be seen that a list of questions there, have not been used for these reasons.

Those symptoms which have been recorded, are set out in Table 8. A number of them require further clarification.

Under the heading "tiredness", notice has been taken only if the mother stated that the child wished to lie in bed during the day.

Included in "other hysterical symptoms" are psychogenic disorders of consciousness and attacks of different kinds, malingering, and similar, but not a hysteroid personality.

"Speech disorders" have, for the most part, consisted of delayed or non-existent development of speech, stuttering and more serious articulation disorders. On the other hand, milder symptoms, such as

TABLE 8. *Presenting symptoms in the subjects grouped according to sex and age.*

Sex	Age	No.	Presenting symptoms																							Total no. of symptoms	Symptoms per case
			a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q	r	s	t	u	v	x	y	
Boys	4–6	36	0	0	2	0	4	2	1	1	1	10	3	10	6	3	4	7	14	6	7	1	1	3	4	1	91	2.5
	7–9	34	1	4	3	0	3	4	0	1	1	9	2	5	10	2	6	2	17	9	12	1	4	3	8	0	107	3.2
	10–12	43	3	9	12	3	3	9	2	0	6	2	1	3	6	0	4	6	17	9	7	0	6	5	8	1	122	2.8
	4–12	113	4	13	17	3	10	15	3	2	8	21	6	18	22	5	14	15	48	24	26	2	11	11	20	2	320	2.8
Girls	4–6	27	1	0	3	0	1	0	0	0	3	6	0	3	1	3	2	6	10	0	6	0	1	1	2	0	49	1.8
	7–9	39	3	2	13	2	2	2	4	2	1	4	0	2	4	2	4	5	14	4	8	2	1	2	4	0	87	2.3
	10–12	50	4	12	20	3	9	12	5	1	7	6	0	2	6	4	4	8	25	9	13	4	9	6	9	2	180	3.6
	4–12	116	8	14	36	5	12	14	9	3	11	16	0	7	11	9	10	19	49	13	27	6	11	9	15	2	316	2.7
	Total	229	12	27	53	8	22	29	12	5	19	37	6	25	33	14	24	34	97	37	53	8	22	20	35	4	636	2.8

a = Tics
b = Headache
c = Abdominal pain
d = Heart symptoms
e = "Growing pains", joint pain
f = Tiredness
g = Nausea, vomiting
h = Confabulation, pathological lying
i = Other hysterical symptoms
j = Enuresis
k = Encopresis
l = Speech disorders
m = Motor restlessness
n = Anorexia, refusal to eat
o = Night terrors
p = Other sleep disorders
q = Emotional lability
r = Difficulties in concentration
s = Anxiety
t = Obsession-compulsion symptoms
u = Depression
v = Aggression
x = Difficulties with companions
y = Unsociability

TABLE 9. *Presenting symptoms in the subjects divided into physical and non-physical.*

Presenting symptoms	Age in years	Boys (B) Total no.	Boys (B) Symptoms per case	Girls (G) Total no.	Girls (G) Symptoms per case	Difference B–G
Physical	4–6	36	0.1	27	0.2	0
	7–9	34	0.4	39	0.7	0
	10–12	43	0.9	50	1.1	0
	4–12	113	0.5	116	0.7	0
Non-physical	4–6	36	2.4	27	1.7	0
	7–9	34	2.8	39	1.6	0
	10–12	43	2.2	50	2.5	0
	4–12	113	2.4	116	2.0	0

lisping and nasal speech were not recorded.

"Other sleep disorders" comprised difficulties in falling asleep (fell asleep after 10 p.m.) or early wakening (before 5 a.m.).

Attacks of pure anxiety without direct relation to the environment have been included under "anxiety".

Adaptation difficulties of such a degree that the child has been isolated have been considered "difficulties with companions".

Finally, pilfering, truancy, vagrancy and the like, which occurred repeatedly and led to action by the parents or the teacher have been included under "unsociability".

In Table 8, the subjects' symptoms are set out according to sex and age. The table shows that such symptoms occur as often in boys as in girls. The 113 boys have 320 symptoms, i.e. 2.8 symptoms per case, while the 116 girls had 316 symptoms, i.e. 2.7 symptoms per case.

In the boys the frequency of symptoms was largely the same in the three age groups, 4–6, 7–9 and 10–12 years of age, viz. 2.5, 3.2, and 2.8 symptoms per case. On the other hand, in the girls, the symptom-frequency rose with increase in age. The number of symptoms per case in these three age groups were 1.8, 2.3, and 3.6. Thus in the eldest group of girls the symptom-frequency per case was the double that in the youngest group.

In the controls the tendency was the opposite for both sexes. The youngest boys had an average of 1.0 symptoms per case, the eldest 0.2, the youngest girls 1.6 symptoms per case, and the eldest 0.6. Gedda (1953), who examined Swedish school children, seven and 11 years old to find out the frequency of nervous symptoms obtained a similar result. The frequency decreases rather than increases with rise in age.

The above symptoms, in the subjects, are set out in Table 9, divided into two groups. In one group, symtoms such as tics, headache, abdominal pain, heart symptoms, tiredness and nausea, vomiting, were put, i.e. physical symptoms. The other group consisted of other symptoms, i.e. those more directly mental in nature.

The table shows that the physical symptoms are uncommon in the youngest age group, but that they become more common with increasing age among both boys and girls. The remaining symptoms occur in largely the same frequency in the various

TABLE 10. *The frequency of presenting symptoms in the subjects and the controls.*

Symptom	a	b	c	d	c–d	C	Significance
Tics	0	158	5	0	5	0.03	—[1]
Headache	0	143	19	1	18	0.11	***
Abdominal pain	2	112	36	13	23	0.14	**
Heart symptoms	0	155	7	1	6	0.04	0
"Growing pains", joint pain	0	147	13	3	10	0.06	*
Tiredness	0	143	20	0	20	0.12	***
Nausea, vomiting	0	151	12	0	12	0.07	***
Confabulation, pathological lying	0	158	5	0	5	0.03	—[1]
Other hysterical symptoms	0	148	12	3	9	0.06	*
Enuresis	4	128	23	8	15	0.09	*
Encopresis	0	160	3	0	3	0.02	—[1]
Speech disorders	1	144	14	4	10	0.06	*
Motor restlessness	0	132	22	9	13	0.08	*
Anorexia, refusal to eat	1	147	12	3	9	0.06	*
Night terrors	1	143	14	5	9	0.06	0
Other sleep disorders	1	127	28	7	21	0.13	***
Emotional lability	7	87	61	8	53	0.33	***
Difficulty in concentration	1	134	20	8	12	0.07	*
Anxiety	2	114	37	10	27	0.17	***
Obsession-compulsion symptoms	0	157	4	2	2	0.01	—[1]
Depression	0	150	12	1	11	0.07	**
Aggression	0	149	14	0	14	0.09	***
Difficulties with companions	1	132	23	7	16	0.10	**
Unsociability	0	159	4	0	4	0.02	—[1]

[1] Signifies that the estimation of significance was not made because of the small size of the groups.

a = number of pairs where both the subject and the control have the symptom.
b = number of pairs where neither has the symptom.
c = number of pairs where only the subject has the symptom.
d = number of pairs where only the control has the symptom.
C = c–d, in %, in all the pairs examined.

age groups. Even such symptoms as enuresis, night-terrors, anorexia-refusal to eat and speech disorders, which one would imagine to be more common in the youngest than in the oldest group, shows no tendency to decrease among the older girls.

If the individual symptoms are examined certain sex differences are noticed.

Encopresis occurred only in six boys.

Speech disorders occurred numerically more often in boys than in girls (18 boys and 7 girls—, i.e. 16 % and 6 % respectively). The difference is almost significant (10 ± 4.1). That stuttering is predominantly met with in boys, was previously described by Geisler (1955) and others.

Motor restlessness was seen in 22 boys and eleven girls, i.e. 19 % and 9 % respectively (Difference 10 ± 4.6).

On the other hand, abdominal pain was recorded more often in girls than in boys. The symtoms occured in 17 boys and 36 girls, i.e. in 15 % and 31 % of the total respectively. The difference is statistically significant (16 ± 5.6). Several authors have previously pointed out that abdominal pain of the type "conversion hysteria", occurs more commonly in girls than in

boys (Apley & Naish 1958, Hinman 1958, Szutrely & Tomory 1958, Apley 1959 etc.).

The remaining symtoms occurred in much the same frequency in both boys and girls.

The 163 subject-control pairs were compared later in pairs with regard to the frequency of presenting symptoms. The result of this is set out in Table 10.

This table shows that all the symptoms are found more often in the subjects than in the controls. Seven symptoms, viz. tics, tiredness, nausea-vomiting, confabulation, encopresis, aggression and unsociability occur only in the subjects.

The probability that the differences found were caused by chance was estimated by a sign-test (Dixon & Massey 1957). Only those pairs were studied in which subject or control had the symptom in question. Those pairs in which neither or both of the members had the symptom were thus not included.

A highly significant difference ($p < 0.1\,\%$) was found to exist in seven symptoms, namely headache, tiredness, nausea-vomiting, "other sleep disorders", emotional lability, anxiety and aggression.

A significant difference ($0.1\,\% < p \leqslant 1\,\%$) existed for three symptoms, viz. abdominal pain, depression and difficulties with companions.

A almost significant difference ($1\,\% < p \leqslant 5\,\%$) occurred with seven symptoms, viz. "growing pains", "other hysterical symptoms", enuresis, speech disorders, motor restlessness, anorexia-refusal to eat, and difficulty in concentration.

Two symptoms, heart symptom and night terrors were not found more often among subjects than among controls ($p < 5\,\%$). No estimation of significance could be carried out on the remaining five symptoms, because of the small size of the groups. Four of these latter symptoms occurred only in isolated cases among the subjects, and not at all among the controls.

Summary

The presenting symptoms are set out. The average number of symptoms per case was 2.8 for boys and 2.7 for girls. Among the boys, the symptoms were divided fairly evenly in the various age groups, while among the girls, the symptom-frequency increased with age. Physical symptoms were found more often among girls than among boys, and seldom among the younger children. They increased with age. Certain sex differences were found: encopresis occurred only in boys. With regard to speech disorders and motor restlessness there was a tendency towards a higher frequency in boys (difference almost significant), while diffuse abdominal pain appeared in a significantly higher frequency in girls than in boys. When the subjects' and the controls' series were compared, it was seen that all the symptoms occurred more often in the former than in the latter. Seven symptoms appeared only among the subjects. There was a significant difference in ten of the 24 symptoms, and an almost significant difference in seven.

Mental condition on examination

When assessing the mental condition of the children, no notice was taken of the history, but only of the mental behaviour at the examination. Even if the history suggested the presence of neurosis, the child was judged to be mentally normal if the author did not find any mental ab-

TABLE 11. *The mental status of the subjects.*

Mental status	Age in years	Boys (B) Total no.	%	Girls (G) Total no.	%	Difference B–G
Symptom-free	4–6	36	39	27	56	0
	7–9	34	38	39	38	0
	10–12	43	33	50	30	0
	4–12	113	36	116	39	0
Mild mental symptoms	4–6	36	36	27	15	*
	7–9	34	32	39	38	0
	10–12	43	40	50	34	0
	4–12	113	36	116	31	0
Mentally insufficient[1]	4–6	36	25	27	30	0
	7–9	34	29	39	23	0
	10–12	43	28	50	36	0
	4–12	113	27	116	30	0

[1] There were 28 cases of anxiety neurosis, 19 of depression, 8 of hysteria, and 4 of obsession-compulsion neurosis. In 7 cases the symptoms could not be satisfactorily classified.

sufficiency. On the other hand, some children were diagnosed as mentally insufficient, in spite of the fact that the history was completely negative.

Those children have been called symptom-free, who on examination appeared relaxed and spontaneous, were easily approached, had a normal emotional tone, showed gentle and refined feelings and seemed to be at a normal stage of maturity.

By mild mental symptoms were meant anxiety and uneasiness in connection with the examination, vegetative symptoms such as fibrillary twitches round the eye and mouth, tense movements, etc. and generalised motor restlessness. The emotional tone has however been normal, contact good and general degree of maturity normal for the age.

The mentally insufficient were tense, anxious and uneasy to a high degree throughout the examination, they were often depressed, their emotions easily roused and coarse, and the contact disturbed. As a rule, they appeared to be immature for their ages.

Of the 229 subjects, 86 (41 boys and 45 girls, i.e. 38 %) were recorded as symptom-free, 77 (41 boys and 36 girls, i.e. 34 %) had mild mental symptoms and 66 (31 boys and 35 girls, i.e. 29 %) were judged as mentally insufficient. The mental condition of the subjects is set out in Table 11, the material being grouped according to sex and age.

The table shows that about one third of the material was mentally symptom-free, one third had mild mental symptoms and one third was judged as mentally insufficient. No significant differences existed between the sex and the different age groups.

The mentally insufficient subjects were classified into five groups. Isolated cases have often been difficult to classify, since the symptom-picture varied and changed from day to day. Generally, the classification was made from the dominating symptom at examination. The 66 men-

tally insufficient were grouped according to the following syndromes.

The anxiety syndrome has been found in the following 28 cases (14 boys and 14 girls): cases 4, 11a, 12a, 12b, 27, 31, 32c, 39b, 49a, 53, 60a, 70a, 72, 77, 81a, 83a, 84b, 90b, 96b, 102b, 103a, 109, 111, 115, 118, 140a, 141a and 141b. The following case is an example:

Case 31: Boy, born 1951. Pregnancy and delivery normal. Birth weight 3500 g. Breast fed six months. Walked early and mental development normal. On the whole, physically well. Always oversensitive, "cries for nothing", "twitches over his whole body if something is said to him". Afraid of the dark, cannot be left alone. Cannot tolerate upsets around him, afraid of children of his own age and cries if they fight. Recent years, tics. Often gets abdominal pain when he is excited or harassed. Unable to be placed in a day-nursery as the mother wished, had an attack of anxiety when this was tried.—On examination: general condition good, but thin. Vegetative signs of nervous instability. Tics around the eyes. Mentally tense, anxious, full of fear. Twitches over the whole of his body as soon as he hears a loud noise. Intellectually normal.

There were depressive symptoms in the following 19 cases (9 boys and 10 girls): cases 20b, 26, 33a, 35c, 36a, 43a, 44b, 47, 50, 55, 62, 70b, 70c, 70d, 76b, 83b, 91a, 93 and 97a. The symptom-picture can be seen from the following case:

Case 50: Girl, born 1946. Pregnancy and delivery normal. Birth weight 3500 g. Breast fed ten months. Walked early and mental development normal. Physically healthy. Mentally always sensitive, cried easily and was quickly depressed. For a number of years, especially when harassed, etc., developed pressure headache or abdominal pain, sometimes very intense and accompanied by nausea and vomiting. In 1951, out-patient examination normal. In 1953 was operated for suspected appendicitis. The appendix was normal and the symptoms remained largely unchanged. In the last years, is sometimes allowed to go home early from school, where she gets on well apart from this. Has recently appeared depressed according to the teacher.—On examination: physically normal. Depressed with psychomotor inhibition. Normal intelligence. Asthenic.—Referred to the child-guidance clinic.

In the following eight cases (3 boys and 5 girls) the symptoms were considered to be hysterical: cases 46, 67, 100, 117, 119a, 122b, 123b and 137). The following is a typical example:

Case 117: Girl, born 1948. Pregnancy normal. Forceps delivery at full term. Birth weight 2670 g. At first sucked weakly and was apathetic, later normal feeding. Walked early and mental development normal. Physically well. Mentally, motor restlessness, inability to concentrate and unstable. Poor contact with companions. Before she started school, she often lay on the floor and kicked if frustrated in her desires. In the previous year, peculiar attacks, hysterical in type.—At present, under treatment at the child-guidance clinic.—On examination: physically normal. Mentally, tense, motor restlessness, no contact. Completely immature. Intellect normal.

Finally, anancastic-coloured symptoms were found in four children (1 boy and 3 girls), cases 15, 51a, 57a and 84a. Here is an example:

Case 84a: Girl, born 1948. Pregnancy and delivery normal. Birth weight 3570 g. Breast fed for one month. Walked early and mental development normal. Previously well physically. Mentally, always very sensitive and nervous. Periodical night terrors. Under mental strain, abdominal pain or pure anxiety. Keeps her own company. Afraid of the dark. She always has to know that the door

is locked. Cannot stay indoors with drawn curtains. Often checks that her mother is at home, that the windows are fastened, etc.—On examination: physically normal. Mentally, tense, anxious, motor restlessness. Difficult to approach. Intellect normal.

In seven cases (4 boys and 3 girls) the symptoms were atypical: cases 14a, 23, 40a, 41, 75, 99c and 114a. Cases 14a, 23 and 114a have been described earlier (see pages 43, 46 and 42). The others are set out below:

Case 40a: Boy, born 1950. Pregnancy and delivery normal. Birth weight 4070 g. Breast fed 5–6 months. Walking development normal. Began to speak at the normal time. Is still wet, both at night and during the day. Physically well, on the whole. Mentally, sensitive, quiet, without friends. Keeps very much to himself.—On examination: physically normal. Mentally, suppressed, quiet, difficult to approach. Intellect normal.

Case 41: Boy, born 1953. Pregnancy and delivery normal. Birth weight 3500 g. Breast fed for nine months. Early walking development normal. Still neither clean nor dry. Stutters. Motor restlessness. Wakes early in the morning. Physically well previously.—On examination: physically normal. Mentally, motor restlessness, difficult to approach. Intellect difficult to assess, probably normal.

Case 75: Boy, born 1953. Pregnancy and delivery normal. Birth weight 3400 g. Breast fed 1½ months. Walked early and mental development normal. Physically healthy. Motor restlessness, inability to concentrate. Stutters. Bed-wetter.—On examination: physically normal. Mentally, tense, anxious, suppressed and unsure. Speech badly developed. Childish for his age. Intellect difficult to assess, probably normal.

Case 99c: Girl, born 1954. Pregnancy and delivery normal. Birth weight 3500 g. Bottle-fed. Walked early and mental development normal. Physically healthy. Mentally normal, but still enuretic, both by day and at night.—On examination: physically normal. Mentally, suppressed, retarded, intellect probably poor.

The different types of insufficiency were distributed among the various age groups, 4–6, 7–9, 10–12 years respectively, as follows:

Anxiety syndromes were on the whole evenly distributed, 8, 10 and 10 cases respectively. The depressions appeared predominantly in the oldest age group, in which there were eleven cases, seven cases appeared in the middle group and only one in the youngest group. Of the eight kinds of hysteria, four were found in the youngest group and for in the oldest. The anancastic-coloured symptoms occurred in three of the oldest group and one of the middle group.

Comparison of the mental states of the matched subject-control pairs brought out the following: Mild mental symptoms were present among subjects alone in 45 pairs, among controls alone in 20 pairs and among both subjects and controls in 10 pairs. Statistically, the difference is almost significant ($1\ \% < p \leqslant 5\ \%$).

Mental insufficiency was found in subjects alone in 39 pairs, in controls alone in four pairs and in both in four pairs. The difference is highly significant ($p < 0.1\ \%$).

Two subjects were judged to be imbeciles. One of the two, a boy, born in 1951, had just been placed in a home for imbeciles at the time of the examination (Case 22, described on p. 42). The other case (Case 23, described on p. 46), also a boy born in 1953, had been examined at the child-guidance clinic just before the examination, and was there recommended for a place in a home for imbeciles. Not one of the controls was so severely mentally retarded.

Nine of the subjects (4 boys and 5 girls, 4 % of the total) were considered to be feeble-minded. Three of these were in the special class, five were too young to go to school and one had had schooling deferred because of immaturity. Six of the controls (4 boys and 2 girls, i.e. 4 % of the total) were considered to have a corresponding level of intelligence. Thirteen subjects (6 %) and six controls (4 %) were denoted as border line cases between mental defect and normal intellect. The remainder were considered to be intellectually normal.

When the intellectual status of the subjects and the controls was compared at the time of the examination, an almost complete agreement was arrived at. Of course, this could be expected since the selection of controls had been made using as one of the principles, similarity between the school reports of subjects and controls. In addition, agreement was very good in the children who had not yet begun school. These latter consisted of 89 subjects (51 boys and 38 girls) and 73 controls (41 boys and 32 girls). Two subjects (boys), but no controls, were regarded as imbeciles, while six subjects (3 boys and 3 girls) and two controls (girls) were considered to be feeble-minded. Four subjects (3 boys and 1 girl) and three controls (1 boy and 2 girls) were assessed intellectually as "borderline". The remainder were considered to have a normal intellectual development.

Summary

Thirty eight per cent of the subjects were judged as mentally normal, 34 % had mild mental symptoms and 29 % were mentally insufficient. The numbers of boys and girls were largely the same in all groups. The mental insufficiencies consisted largely of anxiety neurosis and depressions. On comparing the subjects with the controls, it was confirmed that the mental insufficiencies occurred more frequently among the former, to a highly significant degree. Between four and five per cent of both subjects and controls were considered to be mentally retarded. There were two subjects who were imbeciles, but none of the controls were judged to be so.

Opinion of the teacher

Finally, a further assessment of the mental state of the school children was obtained from the teachers. They were asked to give information on both whether the child was atypical in his general behaviour and on whether he had shown noticeable mental symptoms at school during the past term. Thus, it was not a question of the child's ability to follow the lessons, i.e. of judging the intellectual capacity. In isolated cases it proved to be difficult or impossible to distinguish between the various kinds of difficulties. In these cases the teachers constantly reported the children abnormal. In the majority of cases it was possible to give an opinion from both the above points of view.

Sixty seven subjects (34 boys and 33 girls) who were at school at the time of the investigation were described by the teacher as mentally abnormal, i.e. 48 % of the total. These were distributed in such a way that the highest frequency of abnormality was found among the younger, 7–9-year-old boys (74 % abnormal). In the other groups the frequency on the

whole is on a similar level, (39 %–46 %). The difference is significant (30 ± 11.0).

On comparing the matched subject-control pairs, it appears that in 39 pairs only the subject has been considered abnormal by the teacher, in seven only the control and in ten, both subject and control. The difference between the frequency of abnormality between subject and control is highly significant ($p < 0.1$ %).

Summary

At the time of the investigation the teachers considered 48 % of the subjects who were at school to be abnormal in their general behaviour. This was especially so in the case of the youngest boys of whom 74 % were considered to be abnormal. On comparing them with the controls the difference was highly significant.

Comparison between the results of the different assessments of mental condition

Although the opinion of the teachers in many cases gives a good picture of the subjects' mental condition, in other cases it has been misleading, either because certain appearances were wrongly interpreted as pathological, or because on examination, certain obvious psychopathological symptoms were not noted.

Of the 43 subjects who were at school (20 boys and 23 girls), and on examination were assessed as mentally insufficient, the teachers described only 29 cases (14 boys and 15 girls) as mentally abnormal. Fourteen cases (6 boys and 8 girls) were described by the teachers as normal in their behaviour, in spite of the fact that on examination they were described as mentally insufficient (cases 20b, 26, 32a, 57a, 60a 72, 84a, 96b, 97a, 103a, 119a, 123b, 140a and 141a). Of these, cases 32a, 57a, 84a, 97a, 119a, 123b and 140a have been described previously (pages 43, 60, 44, 47 and 42). The remainder are set out below.

Case 20b: Boy, born 1946. Pregnancy and delivery normal. Birth weight 4300 g. Breast fed for nine months. Walked early and mental development normal. Physically healthy. Mentally oversensitive, cries easily. Often has diffuse abdominal pain when nervous. Tics.—On examination: Physically normal. Mentally inhibited and uncertain. Stutters. Almost asthenic in type.

Case 26: Girl, born 1947. Pregnancy and delivery normal. Birth weight 3400 g. Breast fed for four months. Walked early and mental development normal. Previously healthy physically. Often complained of headache and pain in the legs recently. Night terrors, wants to sleep with the mother. —On examination: physically normal. Mentally, tense and anxious, obviously depressed and inhibited. Intellectually normal.

Case 60a: Boy, born 1948. Pregnancy normal. Twin birth. Birth weight 2250 g. Breast fed for two-three months. Development normal. Physically healthy. During the last year often headache, sometimes with nausea. These come especially often in association with emotional outbursts. Mentally unstable, full of anxiety. Difficulty in falling asleep. Finds agreement with companions difficult.—On examination: physically normal. Mentally, subdued, anxious, uncertain.

Case 72: Boy, born 1949. Pregnancy and delivery normal. Birth weight 3590 g. Breast fed for six months. Walked early, mental development normal. Previously was in a fever hospital with scarlet fever. Otherwise healthy. Mentally over-sensitive, cries easily, motor restlessness, inability to concentrate. Terrified of the dark. Still sucks his thumb. Stutters.—On examination: physically normal. Mentally, tense, anxious, unable to concentrate, motor restlessness. Stutters. Almost asthenic in type.

Case 96b: Girl, born 1950. Pregnancy and delivery normal. Birth weight 3450 g. Breast fed for six months. Walked early and mental

development normal. Was in a childrens' hospital in 1953, with a diagnosis of phlyctenular kerato-conjunctivitis, otherwise healthy. For the last six months frequent abdominal pain, waking at night and crying at least once a week. Doctor on duty was sent for. Restless sleep. Very sensitive.—On examination: physically normal. Mentally, tense, subdued, depressed, poor contact. Intellectually normal.

Case 103a: Boy, born 1945. Pregnancy and delivery normal. Birth weight 4215 g. Breast fed for four to five months. Walked early and mental development normal. Was in a fever hospital with scarlet fever, otherwise healthy. For about six months has been having palpitations and feelings of suffocation, but otherwise no heart symptoms. Visited the doctor who could not find anything organically wrong on examination. Over-sensitive and irritable. Finds difficulty in falling asleep at night. Night terrors.—On examination: physically normal. Mentally, depressed, subdued. Intellectually normal.

Case 141a: Girl, born 1946. Pregnancy and delivery normal. Birth weight 2660 g. Breast fed for four months. Walked early and mental development normal. Previously visited a childrens' hospital with asthmatic bronchitis, now symptom-free. According to the history, quite normal mentally.—On examination physically: vegetative symptoms. Mentally, tense, full of anxiety, bad contact. Asthenic. Intellectually normal.

Of these 14 cases which the teachers failed to observe, six have shown a picture of depression and four have had predominantly physical symptoms. These can be regarded as a natural oversight. The symptom picture in the one group is meagre and inconspicuous and the child is not disturbing to the group In the other group, the symptoms point more to physical than to mental illness. In one case, no history was given of mental symptoms, but in spite of this, on examination, the subject was considered mentally insufficient. It can well be said that this state of insufficiency was of relatively recent origin, and that this could explain the discrepancy in the opinion. On the other hand, it was more difficult to explain that three clear cases of neurosis, all with prolonged history (cases 84a, 119a and 123b), of whom two were under treatment at the child-guidance clinic, had been interpreted by the teachers as normal.

The teachers had described 36 subjects (18 boys and 18 girls) as mentally abnormal, without any symptom of mental insufficiency being found on examination. However, in 23 cases (12 boys and 11 girls) mild mental symptoms were found on examination and in eleven cases (4 boys and 7 girls) nervous symptoms were mentioned in the history. Two boys had been described by the teachers as mentally abnormal without there being any support for this from the history or from the mental condition.

All except three of the cases who were described as mentally insufficient on examination had a history of mental symptoms. The three cases described as mentally insufficient without having a history of mental symptoms are set out below.

Case 49a: Girl, born 1951. Pregnancy and delivery normal. Birth weight 3850 g. Breast fed for twelve months. Walked early and mental development normal. Previously mentally and physically healthy.—On examination: physically normal. Mentally, timid, tense, cries desperately the whole time. Difficult to examine. Probably intellectually normal.

Case 53: Boy, born 1952. Pregnancy and delivery normal. Birth weight 4500 g. Breast fed for ten months. Walked early and mental development normal. Previously healthy physically and mentally.—On exa-

mination: Physically normal. Mentally, tense, timid, full of terror, cries desperately. Motor restlessness. Fibrillary twitches around the eyes. Probably intellectually normal.

Case 141a: Girl, born 1946. Case described on p. 64.

Summary

In 14 cases the teachers considered children to be mentally normal who were designated as mentally insufficient on examination. Of these, six had symptom-pictures of depression and four had predominantly physical symptoms of psychogenic origin. Three cases not identified by the teachers had had prolonged neuroses, of whom, two had been under psychiatric treatment. Only two boys were described by the teacher as abnormal without the mental condition or the history supporting this. Only three of the subjects were designated as mentally insufficient without the history suggesting this. Thus, in the majority of cases the history and the examination were in close agreement on this point.

Discussion

It was shown in Chapter III that nervous manifestations occurred more often in the subjects than in the controls. In spite of this, the former did not come for psychiatric examination and treatment more often than the latter. This is probably due not only to the children themselves, but also to the parents.

All the subjects' fathers could be described as mentally insufficient, and in addition, not a few of them were mentally defective and asocial. As a consequence of this, heavy demands were made on the mothers, who, in many cases, were forced to take over the whole burden of supporting the family. This, not infrequently, caused the mothers to collapse, which, in turn, produced mental insufficiency or led to a divorce. Examination of the mothers did not indicate that they were a particularly weak group. As well as behaving asocially the fathers showed antisocial attitudes. Because of intervention by the authorities, such as being taken into custody and placed in institutions, etc., they developed aggressive and suspicious attitudes towards other forms of social care. This attitude was often transferred to other institutions, not concerned with problems of alcohol, such as the child-welfare centres and child-guidance clinics. As a result of this, only about one half of the subjects took advantage of the free consultations at the child-welfare centres, as against a frequency of about 90 % among normal children. In those cases where the parents consulted the child-guidance clinic about their children, the parents co-operated badly throughout, and often broke off the treatment of the child before it was completed. For the chronic alcoholic, it seemed vital to hide his alcoholism from the social authorities, probably because of fear of repercussions from society. In this respect, the mothers often solidly upheld the fathers. Although other questions in the history received reliable answers as a rule, this was rarely the case with regard to the father's alcoholism. It is probable that the fathers brought pressure of some kind to bear in this connection. In certain cases the mothers' information about the domestic situation points to this fact. In a number of cases the mothers were persuaded either by pleas or threats to resume married life with the father after a short separation.

Sometimes they did not even dare to petition for divorce. The mothers' state of mental insufficiency probably contributed towards this state of affairs. Thus, of 45 mothers described as mentally insufficient, only one (who was psychotic), was under medical care. The others had accepted their symptoms or lacked the strength to ask for help. Possibly the parents' mental insufficiency contributed to their lack of interest in the childrens' state of health. The subjects, therefore, had a significantly higher incidence of bad teeth, in spite of the fact that all children in Sweden are entitled to free dental care.

The subjects themselves are also partly responsible however, for the relative infrequency with which they received psychiatric examination and treatment. According to Henry (1947) and Nylander (1959) in a number of cases of "conversion hysteria" an atmosphere of anxiety exists in the home. Follow-up examinations of hysterical children also revealed that children with such symptoms are liable to be admitted unnecessarily to hospital, and operated, instead of receiving psychotherapy (Purtell, Robins & Cohen 1951, Robbins & O'Neal 1953, Ekström & Nylander 1959 etc.) Twenty two per cent of the presenting symptoms in the subjects were physical or of the type "conversion hysteria". As set out above, this often resulted in admission to or examination at an ordinary hospital, instead of at a psychiatric department or child-guidance clinic.

Some of the responsibility for the neglect of these children with nervous manifestations falls on the social authorities. It is clear from this chapter that only a small number of all the cases of alcoholic fathers which are reported to the Temperance Board come to the notice of the Children's Care Committee. Because of this the authorities have not even the theoretical possibility of examining, and, if necessary, helping the children of these fathers. Even in those cases where the fathers' alcoholism is reported to the Children's Care Committee, measures are taken which cannot be considered satisfactory in helping the children. Those measures which are taken are, most often, much too stereotyped and impermanent. Thus supervision of the alcoholic father stops most often, just when he shows a will to improve, and the child is not competently examined or regarded as important. In order that children of chronic alcoholics may receive the help they need from the point of view of mental health, increased co-operation is required between the authorities dealing with the care of alcoholics and those dealing with the care of children. In addition, more thorough and lasting methods are needed from the Children's Care Committee.

The first two questions put by the author are thereby answered. Children from homes which are severely disturbed emotionally reveal nervous manifestations more often than children from homes where such disturbances can be presumed not to exist. These nervous manifestations often assumed a special nature in as much as they developed as physical symptoms, which led to admission to an ordinary hospital instead of being brought to the notice of the authorities concerned with the mental care of children and young people.

CHAPTER 4

CLINICAL ANALYSIS

The social and medical aspects of the material were elucidated in the previous chapter. It would appear from this, that nervous manifestations appear more often among the subjects than among the controls. The material will be analysed in this chapter in an attempt to make clear whether special factors can be shown to have a more positive importance in the appearance of these nervous manifestations.

With the complicated circumstances, social and otherwise, which exist when analysing the mental factors concerned, the aim cannot be one of establishing complete causal connection. The results which may perhaps be arrived at, must therefore be seen against the background of the possibility of false conclusions, which arise from the complex nature of the problem. All the subjects in this investigation come from homes which are seriously emotionally disturbed. In itself, this can involve such serious stress, that possible influences from other factors in the environment are concealed. Furthermore, the results in analyses of this kind are difficult to interpret because there is a strong negative or positive correlation between many of the environmental factors which can be thought to play an important part in the development of nervous manifestations. Two environmental factors, both strongly represented in the same group can either potentiate each other or cancel each other out, as a result of which it is not possible to judge the importance of the individual environmental factor. However, an analysis of this kind is justified, if by making it, factors can be brought out which to a large extent predominate in one group. Quite often this can lead to findings of practical value.

To analyse the material with these points in mind the author set out in the following way.

From the subjects were chosen on the one hand, all those children, who on examination were mentally symptom-free and assessed as mentally healthy (46 cases), and, on the other hand, all those who were judged as mentally insufficient (66 cases). Both these were later compared with each other concerning the occurrence of a series of different environmental factors, which could possibly be of importance in the development of the illness.

The results of this comparison are set out in Table 12.

It can be seen from the table that only in relation to two environmental factors is there a possibility of a difference in frequency between the mentally symptom-free and the mentally insufficient. These two factors are respectively, that in relation to fathers under the supervision of the Temperance Board and that in relation to broken homes (Parents separated).

TABLE 12. *Comparison between the mentally symptom-free, and the mentally insuf*

Mental status	Sex	No.	Born illegitimate		Mother pregnant at marriage		Parents separated		Mother working		Father drunk every day		Father's intoxication disturbs	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Symptom-free	♂	19	1	5	13	68	4	21	9	47	13	68	13	68
	♀	27	2	7	14	52	8	30	16	59	16	59	16	59
	♂ + ♀	46	3	7	27	59	12	26	25	54	29	63	29	63
Insufficient	♂	31	6	19	14	45	15	48	15	48	22	71	16	52
	♀	35	3	9	19	54	10	29	12	34	21	60	18	51
	♂ + ♀	66	9	14	33	50	25	38	27	41	43	65	34	52

Thus, the frequency of fathers under the supervision of the Temperance Board, is higher among the mentally symptom-free subjects (43 %), than among the mentally insufficient (24 %). The difference is almost significant (19 ± 9.0).

Moreover, the frequency of broken homes is numerically higher among the mentally insufficient boys (48 %), than among the symptom-free boys (21 %). The difference here is also almost significant (27 ± 12.9). However, the frequency of broken homes is largely the same in both groups of girls.

In the following pages, the frequency of nervous manifestations is compared by dividing up the subject material into different sub-groups, which are as follows:

1. Sex and age
2. Social-group
3. Mental constitution and body-build
4. History of brain injury
5. Father's alcoholism
6. Father's contact with the Temperance Board
7. Father's social adaptation
8. Father's state of mental health
9. Father's abstinence from alcohol
10. Mother's state of mental health
11. Mother's employment
12. Number of children in family, position among the siblings
13. Size of the dwelling
14. Broken home
15. The mental condition of the paternal grandparents (alcoholism)
16. The state of mental health of the siblings

Presenting symptoms were compared in the following way: The average number of presenting symptoms was calculated for all the subjects in the respective sub-groups. If one group showed a numerically higher frequency than another, calculation of the significance was made on the difference according to the t-test (Dixon & Massey 1957). In this calculation of significance, only matched subjects were used. On the average, the frequency of presenting symptoms was the same among the subjects with controls, as among those without (see Table 13).

In addition, the matched subjects were always compared with their controls, with regard to the occurrence of the 24 recorded symptoms (see Table 8), divided

insufficient subjects, in terms of the frequency of environmental difficulties etc.

Father alcoholic > 10 years		Father mentally defective		Father under supervision of Temperance Board		Father has had institutional care		Grandfather alcoholic		Mother insufficient		Only child		Family with 4 or more children	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
11	58	4	21	8	42	3	16	7	37	5	26	0	—	6	32
11	41	10	37	12	44	6	22	11	41	7	26	3	11	7	26
22	48	14	30	20	43	9	20	18	39	12	26	3	7	13	28
15	48	4	13	9	29	4	13	16	52	11	35	3	10	6	19
13	37	9	26	7	20	5	14	16	46	14	40	7	20	1	3
28	42	13	20	16	24	9	14	32	48	25	38	10	15	7	11

up into different sub-groups according to the above scheme. The results obtained were later compared with each other. The results were similar unless stated otherwise.

The frequency of mild mental symptoms and mental insufficiency on examination, together with the abnormality as judged by the teacher, were always estimated on all the subjects, even those who did not have controls.

Sex and age

An account of the frequency of nervous manifestations among the subjects, grouped according to sex and age, has already been given in Chapter 3. The average number of presenting symptoms per case was 2.8 for boys and 2.7 for girls. While the frequency of symptoms was largely the same in the different age groups of boys, this increased with age in girls, from 1.8 symptoms per case between four and six years old, to 3.6 symptoms per case between ten and twelve years old. In the matched section of the subjects, the average number of presenting symptoms per case was 2.0 among the youngest and 3.5 among the oldest. The difference is not significant ($5\ \% < p$).

As previously described the frequency of mild mental symptoms and of mental insufficiency on examination, is largely the same in all groups, while the frequency of abnormality as judged by the teacher is higher among the younger boys, than among the older boys and all the girls. The difference is significant.

It is stated in the literature, both foreign (Holman 1953, v. Harnack 1953, Cunningham, Westerman & Fishhoff 1956 etc.) and Swedish (Gunnarson 1946, Gedda 1948, Ahnsjö 1958 etc.), that the majority of nervous symptoms, of such an intensity that medical treatment is required, are found more commonly among boys than among girls. However, in the author's series, the frequency of nervous manifestations is largely the same among both boys and girls.

Summary

The frequency of abnormality as judged by the teacher is significantly higher in boys 7–9 years of age than in boys 10–12 years of age, as well as in all the girls of

TABLE 13. *The frequency of nervous manifestations in the subjects, divided into groups with and without controls, respectively.*

Nervous manifestations	Sex	Subjects with controls (SC) Total no.		Subjects without controls (S) Total no.		Difference SC–S
Symptoms per case	♂	83	2.5	30	3.8	0
	♀	80	2.8	36	2.6	0
	♂ + ♀	163	2.6	66	3.1	0
Mild mental symptoms on examination	♂	83	37%	30	33%	0
	♀	80	33	36	28	0
	♂ + ♀	163	35	66	30	0
Mental insufficiency on examination	♂	83	25%	30	33%	0
	♀	80	29	36	33	0
	♂ + ♀	163	27	66	33	0
Problem child according to teacher	♂	45	58%	17	47%	0
	♀	50	48	28	32	0
	♂ + ♀	95	53	45	38	0

both age groups. Otherwise, however, nervous manifestations appear to an equal extent in the different sex and age groups.

Social groups

The social grouping in the series is set out in Table 2. It can be seen from this that about 83 % of the fathers belonged to group III and only a small number came from groups I + II (38 of the subjects examined).

In social groups I + II, the average number of presenting symptoms per case was 1.4 for boys and 3.0 for girls, while in group III, these were 3.1 for boys and 2.6 for girls.

Mild mental symptoms on examination were found, in boys and girls of groups I + II, to be 25 % and 46 % respectively, while in group III, these figures were 38 % and 28 % respectively.

Mental insufficiency on examination, was diagnosed in boys and girls of groups I + II in 13 % and 23 % respectively, while in group III, the corresponding figures were 30 % and 32 % respectively.

The teacher's judgement was that of abnormality in 50 % of the boys and 38 % of the girls in groups I + II, but 56 % in the boys and 43 % in the girls of group III. With regard to the reliability of the one group, the error of the mean of the above frequencies is large.

Von Harnack (1953) found in an investigation on 7 year-olds in Hamburg, that apart from so-called "vegetative symptoms (pain in the abdomen and trunk, headaches, vomiting and dizziness)", the majority of nervous symptoms were more common in the lowest social groups. Such conditions did not obtain in the social grouping which existed in the author's material.

Summary

No difference can be shown with regard to the frequency of nervous manifesta-

TABLE 14. *The frequency of nervous manifestations in the subjects, divided into asthenic and non-asthenic cases.*

Nervous manifestations	Sex	Asthenic subjects (A) Total no.		Non-asthenic subjects (NA) Total no.		Difference A–NA
Symptoms per case	♂	16	4.6	97	2.5	—
	♀	29	3.5	87	2.5	—
	♂ + ♀	45	3.9	184	2.5	—
Mild mental symptoms on examination	♂	16	50%	97	34%	0
	♀	29	51	87	24	**
	♂ + ♀	45	51	184	29	**
Mental insufficiency on examination	♂	16	50%	97	24%	*
	♀	29	38	87	28	0
	♂ + ♀	45	42	184	26	*
Problem child according to teacher	♂	14	57%	48	54%	0
	♀	26	50	52	38	0
	♂ + ♀	40	53	100	46	0

tions among the subjects, from social groups I + II, compared with those from group III. The number of cases in groups I + II is few and the mean error is large.

Mental constitution and body-build

Several authors have earlier pointed out that asthenic patients have a higher frequency of nervous manifestations than do others (Paskind 1933 and others).

No attempt has been made, to assess the mental constitution of the subjects systematically. At the time of the examination, however, it was regularly noted whether or not the subject was markedly asthenic (Kretschmer 1940) or "subvalid" (Sjöbring 1919). In those cases where a mental insufficiency was present at the time of the examination, this assessment was largely made from the history.

Of the 229 subjects, 45 (16 boys and 29 girls) were judged as being asthenic or "subvalid", i.e. 20 % of the total (cases 7, 8, 11a, 13, 14a, 14b, 17b, 20a, 20b, 27, 33a, 34, 37, 39a, 43a, 44b, 50, 55, 60a, 62, 65a, 72, 74, 78, 79, 81a, 81b, 92a, 106b, 112, 114a, 114b, 118, 119b, 120, 123a, 123b, 130, 131a, 133a, 136a, 140a, 141a, 141b and 142a).

The two groups of subjects, asthenic and non-asthenic, respectively, are compared in Table 14, with regard to the frequency of nervous manifestations. On examination, a significant difference was found among the girls of mild nervous symptoms.

The physical condition of the subjects was not systematically assessed either. However, a rough measurement of this was obtained by using the body-weight. The height was measured, and all cases with a body-weight, which was 3 kilos or more than the average for this height, were put into one group. However, cases whose height exceeded the average (+2.5 sigma over the average height for the age) were not included in this group. Clinically, all these cases were able to be

TABLE 15. *The frequency of nervous manifestations in "under-", "over-", and "normal-" weight subjects.*

Nervous manifestations	Sex	"Underweight" (U) Total no.		"Overweight" (O) Total no.		"Normalweight" (N) Total no.		Difference U–N	Difference O–N
Symptoms per case	♂	19	2.4	15	2.1	71	2.9	0	0
	♀	25	3.5	13	1.8	71	2.6	0	0
	♂ + ♀	44	3.0	28	1.9	142	2.8	0	0
Mild mental symptoms on examination	♂	19	47%	15	40%	71	31%	0	0
	♀	25	40	13	31	71	35	0	0
	♂ + ♀	44	43	28	36	142	33	0	0
Mental insufficiency on examination	♂	19	16%	15	20%	71	37%	−*	0
	♀	25	32	13	15	71	28	0	0
	♂ + ♀	44	25	28	18	142	32	0	0
Problem child according to teacher	♂	11	27%	14	64%	36	53%	0	0
	♀	20	30	9	22	45	49	0	0
	♂ + ♀	31	29	23	48	81	51	−*	0

classified as leptosomatic. There were 44 cases altogether (19 boys and 25 girls) (cases 7, 11b, 14b, 15, 20b, 21, 30a, 31, 32b, 34, 41, 44a, 46, 52, 60b, 61, 69, 76a, 78, 79, 94a, 97a, 102b, 106a, 107b, 108, 109a, 117, 118, 121a, 121b, 122a, 123b, 124, 125a, 126a, 129, 133a, 134a, 138a, 138b, 138c, 140a and 140b). Of the 44 cases, classified as "underweight", only seven were considered to be asthenic or "subvalid" on examination.

For the purpose of comparison, two groups were taken. The one consisted of all those cases whose body-weight exceeded the average weight for the corresponding height by three or more kilos. This group described below as "overweight" consisted of 28 cases (15 boys and 13 girls) (cases 6, 20a, 38a, 43a, 48, 49a, 58, 63, 64, 73, 84a, 86, 96a, 104, 105a, 109, 112, 116a, 116b, 116c, 119a, 119b, 119c, 119d, 125b, 127b, 130 and 131b). The second group comprised the other subjects, described as "normalweight", with the exception of 15 cases (8 boys and 7 girls), who for different reasons could not be weighed and were therefore not included in the analysis of the material (cases 1a, 1c, 3, 22, 23, 30b, 47, 60a, 70a, 70b, 70c, 70d, 98, 100 and 137).

The three groups, "underweight", "overweight" and "normalweight", were compared with regard to the frequency of nervous manifestations (see Table 15). No significant differences could be shown between the groups.

Summary

The constitutionally asthenic or "subvalid", showed a higher frequency of mild mental symptoms, when examined, compared with the non-asthenic. No significant differences appear in the frequency of nervous manifestations among the "underweight" and "overweight" subjects compared with those who were "normalweight".

TABLE 16. *The frequency of nervous manifestations among subjects with and without a history of brain injury.*

Nervous manifestations	Sex	With brain injury (BS) Total no.		Without brain injury (S) Total no.		Difference BS–S
Symptoms per case	♂	23	3.1	90	2.8	0
	♀	16	3.1	100	2.7	0
	♂ + ♀	39	3.1	190	2.7	0
Mild mental symptoms on examination	♂	23	48%	90	33%	0
	♀	16	25	100	32	0
	♂ + ♀	39	38	190	33	0
Mental insufficiency on examination	♂	23	26%	90	28%	0
	♀	16	38	100	29	0
	♂ + ♀	39	31	190	28	0
Problem child according to teacher	♂	13	69%	49	51%	0
	♀	13	54	65	40	0
	♂ + ♀	26	62	114	45	0

History of brain injury

It is stated that brain damage of different kinds not uncommonly gives rise to nervous manifestations in children. Such brain damage can follow infections of the central nervous system, birth injuries, other brain injuries, intoxications, etc. These have been described by Goldstein (1944), Greenebaum & Lurie (1948), Göllnitz (1953), Annell (1953), Bamberger (1957), Harris (1957), etc.

Thirty nine of the author's subjects (23 boys and 16 girls) were suspected of having such damage, in the majority of cases in the form of birth injuries.

These subjects were compared with the remainder, with regard to the frequency of nervous manifestations. The results are set out in Table 16. No differences between the groups could be seen.

Summary

The subjects who were suspected of having a history of brain damage, did not reveal a higher frequency of nervous manifestations than did the other subjects.

Father's alcoholism

In Table 17 an account is given of the frequency of the presenting symptoms, mild mental symptoms and mental insufficiency respectively, together with abnormality as judged by the teacher. The material is divided into groups according to the nature of the father's alcoholism and the way in which the father reacts to alcohol.

The table shows that there are no differences in the frequency of nervous manifestations between the various groups. The average number of symptoms per case in the girls whose fathers have been alcoholics for more than ten years, is 3.2, as against 1.9 in girls whose fathers have been alcoholics for less than five years. However, the difference is not significant.

TABLE 17. *The frequency of nervous manifestations among subjects in relation to the duration and type of alcoholism in the fathers.*

Nervous manifestations	Sex	Duration (a) < 5 years Total no.		Duration (b) 5–10 years Total no.		Duration (c) > 10 years Total no.		Appearance (d) Sporadic Total no.		Appearance (e) Daily Total no.		Type of intoxication (f) Average Total no.		Type of intoxication (g) Disturbing Total no.		Difference a–b	Difference a–c	Difference d–e	Difference f–g
Symptoms per case	♂	17	3.4	42	2.8	54	2.7	44	2.8	69	2.9	46	3.0	67	2.7	0	0	0	0
	♀	16	1.9	55	2.5	45	3.2	50	2.8	66	2.7	54	2.4	62	3.0	0	0	0	0
	♂ + ♀	33	2.7	97	2.7	99	2.9	94	2.8	135	2.8	100	2.7	129	2.9	0	0	0	0
Mild mental symptoms on examination	♂	17	41%	42	43%	54	30%	44	45%	69	30%	46	46%	67	30%	0	0	0	0
	♀	16	38	55	35	45	24	50	38	66	26	54	33	62	29	0	0	0	0
	♂ + ♀	33	39	97	38	99	27	94	41	135	28	100	39	129	29	0	0	*	0
Mental insufficiency on examination	♂	17	35%	42	24%	54	28%	44	20%	69	32%	46	33%	67	24%	0	0	0	0
	♀	16	19	55	35	45	29	50	28	66	32	54	31	62	29	0	0	0	0
	♂ + ♀	33	27	97	30	99	28	94	24	135	32	100	32	129	26	0	0	0	0
Problem child according to teacher	♂	7	71%	18	67%	37	46%	25	56%	37	54%	26	50%	36	58%	0	0	0	0
	♀	10	20	32	47	36	44	30	43	48	42	38	50	40	35	0	0	0	0
	♂ + ♀	17	41	50	54	73	45	55	49	85	47	64	50	76	46	0	0	0	0

TABLE 18. *The frequency of nervous manifestations in the subjects in relation to the father's contact with the Temperance Board.*

Nervous manifestations	Sex	Father not under supervision (a) Total no.		Father under supervision (b) Total no.		Difference a–b
Symptoms per case	♂	70	3.0	43	2.6	0
	♀	80	2.9	36	2.3	0
	♂ + ♀	150	2.9	79	2.5	0
Mild mental symptoms on examination	♂	70	39%	43	33%	0
	♀	80	34	36	25	0
	♂ + ♀	150	36	79	29	0
Mental insufficiency on examination	♂	70	31%	43	21%	0
	♀	80	34	36	22	0
	♂ + ♀	150	33	79	22	0
Problem child according to teacher	♂	37	62%	25	44%	0
	♀	56	43	22	41	0
	♂ + ♀	93	51	47	43	0

Summary

No differences are found in the frequency of nervous manifestations between the groups, with the material divided according to the nature of the father's alcoholism and the way in which the father reacts to alcohol, respectively.

Father's contact with the Temperance Board

In order to find out if supervision of the fathers by the Temperance Board had any influence on the frequency of nervous manifestations in the subjects, the series was divided up into three groups. In the first group were put those children whose fathers were under the supervision of the Temperance Board at the time of the investigation, 79 cases (43 boys and 36 girls). In the second group were put those children whose fathers had previously been under the supervision of the Temperance Board, but at the time of the investigation had been discharged, 74 cases (32 boys and 42 girls). In the third group were put those cases whose fathers were not known by the Temperance Board, 76 cases (38 boys and 38 girls). These groups were then compared for the frequency of nervous manifestations. This showed that the first group differed fundamentally from the other two, which were very similar to each other, so that they were combined to form one group. In this way the series was divided up into two groups. In the one group the fathers were under the supervision of the Temperance Board, while in the other the fathers were in no way supervised by the Temperance Board at the time of the investigation. These two groups were compared for the frequency of nervous manifestations. The results of this comparison are set out in Table 18.

As the table shows, the children of fathers controlled by the Temperance Board show numerically fewer presenting symptoms per case (2.5), than children of

TABLE 19. *Comparison between frequency of symptoms in subjects whose fathers are under the supervision of the Temperance Board, and the controls.*

For explanation of groups indicated by letters see table 10, p. 57.

Symptom	a	b	c	d	c–d	C	Significance
Tics	0	58	2	0	2	0.03	—
Headache	0	55	4	1	3	0.05	—
Abdominal pain	1	43	12	4	8	0.13	0
Heart symptoms	0	58	2	0	2	0.03	—
"Growing pains", joint pain	0	53	5	2	3	0.05	—
Tiredness	0	55	5	0	5	0.08	—
Nausea, vomiting	0	54	6	0	6	0.10	—
Confabulation, pathological lying	0	58	2	0	2	0.03	—
Other hysterical symptoms	0	56	2	2	0	0	—
Enuresis	2	48	7	3	4	0.07	0
Encopresis	0	60	0	0	0	0	—
Speech disorders	1	55	2	2	0	0	—
Motor restlessness	0	46	8	6	2	0.03	0
Anorexia, refusal to eat	0	52	5	3	2	0.03	0
Night terrors	0	55	2	3	−1	−0.02	—
Other sleep disorders	1	47	7	5	2	0.03	0
Emotional lability	5	33	17	5	12	0.20	*
Difficulty in concentration	0	47	8	5	3	0.05	0
Anxiety	1	43	10	6	4	0.07	0
Obsession-compulsion symptoms	0	57	2	1	1	0.02	—
Depression	0	57	2	1	1	0.02	—
Aggression	0	56	4	0	4	0.07	—
Difficulties with companions	0	47	6	7	−1	−0.02	0
Unsociability	0	59	1	0	1	0.02	—

fathers not controlled by the Temperance Board (2.9). However, the difference is not significant.

In Table 19 the matched subjects, with fathers under Temperance Board supervision, are compared with their controls concerning the occurrence of the 24 recorded symptoms. It can be seen that nine of these symptoms could be treated statistically (abdominal pain, enuresis, motor restlessness, anorexia-refusal to eat, other sleep disorders, emotional lability, difficulties in concentration, anxiety and difficulties with companions). Not one of these nine symptoms occurs significantly more often among the subjects than among the controls. (One symptom, emotional lability was found, however, more frequently, to an almost significant degree among the subjects than among the controls.) Two symptoms (night terrors and difficulties with companions), actually occurred numerically more often among the controls than among the subjects.

Similarly, in Table 20, the matched subjects, whose fathers were not under the supervision of the Temperance Board, were compared with their controls. Sixteen of the 24 recorded symptoms could be treated statistically. Eight of these occurred significantly more often among the subjects than among the controls (in depression and aggression the difference was significant, while in the symptoms headache, tiredness, other sleep disorders, emotional lability, anxiety and

TABLE 20. *Comparison between symptoms in subjects whose fathers are not under the supervision of the Temperance Board, and the controls.*

For explanation of groups indicated by letters see table 10, p. 57.

Symptom	a	b	c	d	c–d	C	Significance
Tics	0	100	3	0	3	0.03	—
Headache	0	88	15	0	15	0.15	***
Abdominal pain	1	69	24	9	15	0.15	*
Heart symptoms	0	97	5	1	4	0.04	—
"Growing pains", joint pain	0	94	8	1	7	0.07	*
Tiredness	0	88	15	0	15	0.15	***
Nausea, vomiting	0	97	6	0	6	0.06	—
Confabulation, pathological lying	0	100	3	0	3	0.03	—
Other hysterical symptoms	0	92	10	1	9	0.09	*
Enuresis	2	80	16	5	11	0.11	*
Encopresis	0	100	3	0	3	0.03	—
Speech disorders	0	89	12	2	10	0.10	*
Motor restlessness	0	86	14	3	11	0.11	*
Anorexia, refusal to eat	1	95	7	0	7	0.07	—
Night terrors	1	88	12	2	10	0.10	*
Other sleep disorders	0	80	21	2	19	0.18	***
Emotional lability	2	54	44	3	41	0.40	***
Difficulty in concentration	1	87	12	3	9	0.09	*
Anxiety	1	71	27	4	23	0.22	***
Obsession-compulsion symptoms	0	100	2	1	1	0.01	—
Depression	0	93	10	0	10	0.10	**
Aggression	0	93	10	0	10	0.10	**
Difficulties with companions	1	85	17	0	17	0.17	***
Unsociability	0	100	3	0	3	0.03	—

difficulties with companions, the difference was highly significant). All 24 symptoms occurred numerically more often among the subjects than among the controls.

As shown in Tables 19 and 20, the control cases have, on the average, a numerically somewhat higher frequency of presenting symptoms in the group where the fathers are under the supervision of the Temperance Board (1.1), than in the group where they are not (0.5). This difference may depend on the choice of controls and may indicate that conditions are, in general, worse in the control group of the Temperance Board cases than in the control group of the non-Temperance Board cases. However, this difference between the control groups is not especially large or statistically significant. In any case, it cannot completely explain the differences found between the groups. The author therefore felt it desirable to investigate the circumstances more closely. It is obvious that the distinctions between subjects and controls are difficult to define, if adverse factors exist in the control group. However, this part of the investigation by itself, can never be regarded as decisive when considering if the differences found depend on the supervision of the Temperance Board. Further reliable data is necessary in order to confirm this point. An idea of this was given in the introduction to this chapter. Now, however, the subject series will also be ana-

TABLE 21. *Age groups among the subjects, grouped according to whether or not the father has contact with the Temperance Board (only these subjects had controls allotted to them).*

Age	Father under supervision No.	%	Father not under supervision No.	%
4–6 years	20	33	31	30
7–9 years	19	32	31	30
10–12 years	21	35	41	40
Total	60	100	103	100

TABLE 22. *Duration of father's alcoholism, with the subjects (only those who had controls) grouped according to whether or not the father has contact with the Temperance Board.*

Duration of alcoholism	Father under supervision No.	%	Father not under supervision No.	%
< 5 years	7	12	19	18
5–10 years	25	42	49	48
> 10 years	28	47	35	34
Total	60	101	103	100

lysed for factors which can be thought to cause the differences between the children of the supervised and the non-supervised fathers. It will then be seen that such differences cannot be shown, so that one has no reason either, for assuming any obvious differences in the control group.

The frequency of mild mental symptoms and mental insufficiency, together with the finding of abnormality by the teacher, appear to lend support to the contention that a real difference exists. These values are constantly numerically lower among the subjects, whose fathers are under the supervision of the Temperance Board, than among the subjects whose fathers are not under such supervision. However, the differences here are not significant. On the other hand, if the total frequency of nervous symptoms is estimated, i.e. both mild mental symptoms and mental insufficiency grouped together, the difference, between the group whose fathers are under Temperance Board supervision and the group whose fathers are not, is significant (18 ± 6.8).

Thus it is almost statistically significant that the mentally healthy children, to a larger extent, had fathers controlled by the Temperance Board, than did the mentally insufficient, and it is statistically significant that nervous symptoms on examination occur in a lower frequency in subjects whose fathers are under the supervision of the Temperance Board than in subjects whose fathers are not. Furthermore, when analysing the presenting symptoms in subjects and controls, significant differences are found only in children of fathers not under Temperance Board control.

No explanations of these differences have so far presented themselves through analysis of the environmental factors, which are dealt with in the investigation. For example, age distribution is largely the same among subjects whose fathers are under Temperance Board supervision, as among those whose fathers are not (see Table 21). Neither can a difference in the duration of the father's alcoholism be shown when the two groups are compared (see Table 22). This is also the case with the frequency of daily alcoholism among the fathers. Such alcoholism occurs in 48 % of the Temperance Board supervised

cases, and in 57 % of the non-supervised. Furthermore, mentally insufficient mothers are found in 33 % of the former group and 35 % of the latter group, while broken homes exist in 30 % and 23 % of the families, respectively. Alcoholism, or mental illness in the paternal grandparents was recorded in 57 % of subjects whose fathers were under Temperance Board supervision, and in 49 % of subjects whose fathers were not under such supervision. Demonstrable differences in frequency were not found either in these latter comparisons.

However, significant differences exist between the two groups in relation to two environmental factors which may give rise to nervous manifestations in the children. These factors are, severely disturbing intoxication in the father (difference 40 ± 5.9), and inability of the father to support the family (difference 17 ± 5.4). These factors were not found at all among the controls and the frequency was higher among the subjects, whose fathers were under the supervision of the Temperance Board (82 % and 25 % respectively), than among the subjects, whose fathers were not under supervision.

Because of this, the author is not able to establish that the difference between the frequency of nervous manifestations in the children of fathers supervised and not supervised by the Temperance Board, is dependent on environmental differences between these two groups. Regarding the choice of controls, there is no reason to suppose that there are any obvious environmental differences between the controls of the Temperance Board supervised cases and those of the non-supervised cases. In accordance with this, the author finds that there is a real difference in the frequency of nervous manifestations between the children of Temperance Board supervised and non-supervised fathers.

Since the reason for the lower frequency of nervous manifestations in the children of fathers supervised by the Temperance Board cannot be explained by analysis of the different environmental factors, it must be assumed that the supervision by the Temperance Board is important in itself, and it is easy to suppose that such supervision gives an increased security to the family and thus reacts favourably on the childrens' state of mental health.

Summary

The subjects whose fathers are under the supervision of the Temperance Board show nervous manifestations less often than either those whose fathers have had no contact with the Temperance Board or those previously under the supervision of the Temperance Board, but later discharged. This is in good agreement with what has previously appeared, when comparing subjects mentally symptom-free and mentally insufficient, in relation to the fathers' contact with the Temperance Board. Since other environmental factors could not be shown to have any importance in this respect, it seems that the father's contact with the Temperance Board gives the family the advantage that the child's position is favourably affected, in spite of the fact that among the fathers there is a high frequency of severely disturbing intoxication and inability to support the family.

TABLE 23. *The frequency of nervous manifestations in the subjects in relation to the father's social adaptation (confined to an institution for alcoholics, convicted, or unable to support the family).*

Nervous manifestations	Sex	Father socially maladapted (M) Total no.		Father socially adapted (A) Total no.		Difference M–A
Symptoms per case	♂	40	2.7	73	2.9	0
	♀	45	2.6	71	2.8	0
	♂ + ♀	85	2.7	144	2.8	0
Mild mental symptoms on examination	♂	40	30 %	73	40 %	0
	♀	45	22	71	37	0
	♂ + ♀	85	26	144	38	0
Mental insufficiency on examination	♂	40	28 %	73	27 %	0
	♀	45	31	71	30	0
	♂ + ♀	85	29	144	28	0
Problem child according to teacher	♂	21	62 %	41	51 %	0
	♀	29	31	49	49	0
	♂ + ♀	50	44	90	50	0

Father's social adaptation

The frequency of nervous manifestations among the subjects whose fathers were socially mal-adapted and well-adapted respectively, are set out in Table 23. In the group "mal-adapted", have been included the inability to support the family at the time of the investigation, care at an institution for alcoholics, at the time of the investigation or earlier, and criminality.

No significant differences were found between the two groups.

In the author's series, the number of fathers under the supervision of the Temperance Board is more than twice as high among the socially mal-adapted fathers as among those not socially mal-adapted, 53 % and 24 % respectively. The difference is highly significant (29 ± 6.4). As previously shown, children of fathers who are under the supervision of the Temperance Board, have fewer nervous symptoms than children of fathers who are not under this supervision. It may therefore be thought of importance that the socially mal-adapted, to a larger extent, are under the supervision of the Temperance Board, with the result that differences do not appear.

If, however, a comparison is made between the frequency of nervous manifestations, on the one hand, in subjects whose fathers are under the supervision of the Temperance Board and are socially mal-adapted, and, on the other hand, in subjects whose fathers are under the supervision of the Temperance Board and are better adapted socially, no differences appear either. This indicates that the fathers social adaptability, by itself, cannot be shown to have any great importance in the development of nervous manifestations in the subjects if the Temperance Board has been notified.

TABLE 24. *The frequency of nervous manifestations in the subjects in relation to the mental status of the father.*

Nervous manifestations	Sex	Father deteriorated (D) Total no.		Father non-deteriorated (N) Total no.		Difference D–N
Symptoms per case	♂	23	2.5	90	2.9	0
	♀	31	2.6	85	2.8	0
	♂ + ♀	54	2.6	175	2.8	0
Mild mental symptoms on examination	♂	23	35 %	90	37 %	0
	♀	31	16	85	36	−*
	♂ + ♀	54	24	175	37	0
Mental insufficiency on examination	♂	23	17 %	90	30 %	0
	♀	31	29	85	31	0
	♂ + ♀	54	24	175	30	0
Problem child according to teacher	♂	13	54 %	49	55 %	0
	♀	17	29	61	46	0
	♂ + ♀	30	40	110	50	0

Summary

Children of socially mal-adapted fathers have not shown nervous manifestations to a greater extent than children of fathers who are not socially mal-adapted.

Father's state of mental health

As previously set out, a number of the subjects' fathers revealed mental abnormality on examination. Their children, a total of 54 (23 boys and 31 girls), were compared with children of fathers mentally normal on examination, 175 cases (90 boys and 85 girls) with regard to the frequency of nervous manifestations (see Table 24).

No significant differences between the two groups could be shown, either concerning the frequency of presenting symptoms, mild mental symptoms and mental insufficiency respectively, or abnormality as judged by the teacher.

The frequency of fathers with mental abnormality under the supervision of the Temperance Board was higher (54 %), than among fathers who were not under such supervision (29 %). To find out if this ratio had any effect on the distribution of the nervous manifestations in both groups, the author took out all the children of the fathers under the supervision of the Temperance Board. The frequency of nervous manifestations was compared, on the one side, between cases whose fathers had mental abnormalities, and on the other side, cases whose fathers were mentally normal. No differences could be found between them, however. This indicates that the fathers' mental state, of itself, was not important, if the Temperance Board had been notified.

Summary

Subjects of fathers with mental abnormality, did not show nervous manifestations to a greater extent than those of fathers judged to be mentally normal.

TABLE 25. *The frequency of nervous manifestations in the subjects in relation to the results of treating the father at the Mariapoliklinik.*

Nervous manifestations	Sex	Father who has abstained for 6 months or more (A) Total no.		Father who has not abstained for 6 months or more (NA) Total no.		Difference A–NA
Symptoms per case	♂	13	2.2	100	2.9	0
	♀	18	2.4	98	2.8	0
	♂ + ♀	31	2.3	198	2.8	0
Mild mental symptoms on examination	♂	13	31 %	100	37 %	0
	♀	18	44	98	29	0
	♂ + ♀	31	39	198	33	0
Mental insufficiency on examination	♂	13	31 %	100	27 %	0
	♀	18	17	98	33	0
	♂ + ♀	31	23	198	30	0
Problem child according to teacher	♂	7	43 %	55	56 %	0
	♀	11	45	67	42	0
	♂ + ♀	18	44	122	48	0

Father's abstinence from alcohol

As previously mentioned, the information given by the subjects' mothers concerning the fathers' alcoholism, was often unreliable. In many cases the mother stated that the fathers were no longer alcoholics, but on visiting the home the father might be found drunk. In not a few cases the mothers would also minimise the results of the fathers' alcoholism. In spite of this, the information given by the mothers concerning the fathers' alcoholism, at the time of the investigation, is set out below.

It was indicated that, out of 141 subjects' fathers, only 38, or 27 % of the total, had been completely abstemious for at least a month. Twenty one had totally abstained for at least six months and eight for more than twelve months. In a few of the other fathers, alcoholism was unknown to the mothers, because contact between them was no longer maintained (divorced). The other fathers were said to continue being alcoholics, in spite of treatment from the Mariapoliklinik. Table 25 compares the frequency of nervous manifestations between children of fathers who abstained from alcohol for at least six months and all the others.

The comparison shows that no differences between the frequency of nervous manifestations can be shown between the two groups.

Summary

No differences could be shown between children of fathers, stated by the mothers as having been abstinent from alcohol for at least six months, compared with other children, concerning the frequency of nervous manifestations.

TABLE 26. *The frequency of nervous manifestations in the subjects in relation to the mental health of the mother.*

Nervous manifestations	Sex	Age in years	Mother mentally insufficient (I) Total no.		Mother mentally healthy (H) Total no.		Difference I–H
Symptoms per case	♂	4–6	8	2.6	28	2.6	—
	♀		12	2.4	15	1.2	—
	♂	7–9	15	3.5	19	2.8	—
	♀		5	2.2	34	2.2	—
	♂	10–12	13	3.4	30	2.6	—
	♀		18	4.7	32	3.0	—
	♂	4–12	36	3.3	77	2.6	—
	♀		35	3.6	81	2.3	**[1]
Mild mental symptoms on examination	♂	4–6	8	50 %	28	32 %	0
	♀		12	8	15	20	0
	♂	7–9	15	27	19	37	0
	♀		5	80	34	32	*
	♂	10–12	13	38	30	40	0
	♀		18	28	32	38	0
	♂	4–12	36	39	77	36	0
	♀		35	29	81	32	0
Mental insufficiency on examination	♂	4–6	8	25 %	28	25 %	0
	♀		12	42	15	20	0
	♂	7–9	15	33	19	26	0
	♀		5	—	34	26	0
	♂	10–12	13	31	30	27	0
	♀		18	50	32	28	0
	♂	4–12	36	31	77	26	0
	♀		35	40	81	26	0
Problem child according to teacher	♂	4–6	—	—	—	—	0
	♀		—	—	—	—	0
	♂	7–9	10	80 %	9	67 %	0
	♀		4	—	24	38	0
	♂	10–12	13	46	30	33	0
	♀		18	72	32	41	*
	♂	4–12	23	61	39	41	0
	♀		22	60	56	39	0

[1] Estimated on the matched part of the material.

Mother's state of mental health

Table 26 shows comparison of the frequency of nervous manifestations between, on the one hand, those subjects, whose mothers had been judged as mentally healthy, and, on the other hand, those subjects whose mothers had been judged as mentally insufficient. Since children of younger age groups can be thought to react differently from older children, the material has been divided up into different age groups. The table shows that concerning boys, there are no essential differences between the groups. The number of presenting symptoms, mild mental symptoms and mental insufficiency, together with abnormality as judged by the teacher, are largely the same

TABLE 27. *The frequency of nervous manifestations in the subjects in relation to the incidence of employment among the mothers.*

Nervous manifestations	Sex	Mother working full-time (F) Total no.		Mother working half-time (H) Total no.		Mother not working (N) Total no.		Difference F–N	Difference H–N
Symptoms per case	♂	27	3.2	21	3.1	65	2.6	0	0
	♀	34	2.3	23	2.9	59	2.9	0	0
	♂ + ♀	61	2.7	44	3.0	124	2.8	0	0
Mild mental symptoms on examination	♂	27	44 %	21	24 %	65	37 %	0	0
	♀	34	26	23	43	59	29	0	0
	♂ + ♀	61	34	44	34	124	33	0	0
Mental insufficiency on examination	♂	27	33 %	21	29 %	65	25 %	0	0
	♀	34	26	23	13	59	39	0	− **
	♂ + ♀	61	30	44	20	124	31	0	0
Problem child according to teacher	♂	16	69 %	15	53 %	31	48 %	0	0
	♀	22	36	19	37	37	49	0	0
	♂ + ♀	38	50	34	44	68	49	0	0

among children in all age groups, with healthy or mentally insufficient mothers.

The circumstances are different in relation to girls. Thus, among subjects with mentally healthy mothers, the number of presenting symptoms per case, for the youngest group, was 1.2, for the oldest 3.0, while among subjects with mentally insufficient mothers, the figure for the youngest group was 2.4, and for the oldest 4.7. An estimation of significance was performed on the matched part of the subjects. Statistical analysis of the different age groups culd not be carried out, because of the small numbers involved. The average number of symptoms per case among the girls in all the age groups, was 1.2, where the subject had a mentally healthy mother, and 4.0 where the subject had a mentally insufficient mother. The difference is statistically significant (0.1 % $< p \leqslant 1$ %). The difference cannot be explained by the fathers in those homes where the mother is mentally insufficient, being more often under the supervision of the Temperance Board, than in those homes, where the mother is mentally healthy, since no such significant difference exists. This difference is only 12 ± 8.5.

The girls of mentally healthy and mentally insufficient mothers showed no significant differences with regard to the frequency of mild mental symptoms, mental insufficiency and abnormality as judged by the teacher, but the frequencies are higher throughout among the latter than among the former.

Summary

The frequency of presenting symptoms is higher among those girls in the subjects, who have mentally insufficient mothers, than among those who have mentally normal mothers. The difference is significant. The frequency of other nervous manifestations is higher among the former than among the latter, but the differen-

TABLE 28. *The frequency of nervous manifestations in the subjects in relation to the size of the family.*

Nervous manifestations	Sex	One-child family (O) Total no.		Two- to three-child family (T) Total no.		Four- or more child family (F) Total no.		Difference O–T	Difference O–F
Symptoms per case	♂	11	3.6	72	3.0	30	2.2	0	—
	♀	22	4.2	74	2.7	20	1.2	0	*[1]
	♂ + ♀	33	4.0	146	2.8	50	1.8	0	*[1]
Mild mental symptoms on examination	♂	11	64 %	72	35 %	30	30 %	0	*
	♀	22	41	74	32	20	15	0	*
	♂ + ♀	33	48	146	34	50	24	0	*
Mental insufficiency on examination	♂	11	27 %	72	28 %	30	27 %	0	0
	♀	22	32	74	34	20	15	0	0
	♂ + ♀	33	30	146	31	50	22	0	0
Problem child according to teacher	♂	2	100 %	44	50 %	17	59 %	0	0
	♀	14	79	49	35	14	36	***	*
	♂ + ♀	16	81	93	42	31	48	***	*

[1] Estimated on the matched part of the material

ces are not significant. Among the corresponding boys, no similar differences can be shown. The comparison seems to be of particular interest, in so far as it supports the idea of the mother's special importance in the development of the daughters' personality.

Mother's employment

Table 27 shows the frequency of nervous manifestations among the subjects with the material divided up into three groups; in the first, the mother has full-time employment, in the second, half-time employment and in the third, no employment at all. The table shows that the frequency of mentally insufficient girls is lower in those families where the mother has half-time employment, than in those families where she has no employment at all. The difference is significant (26 ± 9.5). A corresponding difference cannot be shown among the boys.

The frequency of fathers who at the time of the investigation were under the supervision of the Temperance Board, is largely the same in the three groups, i.e. 41 %, 41 % and 34 %.

Summary

Girls from homes where the mother is employed half-time, are less often mentally insufficient, than girls from homes where the mother is not employed at all.

Number of children in family, position among the siblings

The nervous manifestations are set out in Table 28, with the material divided up according to the number of children in the family.

The table shows that nervous manifestations occur in a numerically higher frequency among only children, than among children from larger families. Abnormality as judged by the teacher,

TABLE 29. *The frequency of nervous manifestations in the subjects in relation to the size of dwelling.*

Nervous manifestations	Sex	Subjects living in one room (O) Total no.		Subjects living in more than one room (M) Total no.		Difference O–M
Symptoms per case	♂	13	4.4	100	2.6	—
	♀	16	2.3	100	2.8	—
	♂ + ♀	29	3.2	200	2.7	—
Mild mental symptoms on examination	♂	13	31 %	100	37 %	0
	♀	16	31	100	31	0
	♂ + ♀	29	31	200	34	0
Mental insufficiency on examination	♂	13	46 %	100	25 %	0
	♀	16	31	100	30	0
	♂ + ♀	29	38	200	28	0
Problem child according to teacher	♂	3	100 %	59	53 %	***
	♀	9	56	69	41	0
	♂ + ♀	12	67	128	46	0

appears significantly more often among girls without siblings than among girls with one or two siblings (difference 44 ± 12.8).

The average number of presenting symptoms per case, in the matched part of the subject series, is 3.7 for only children and 2.0 for children from larger families. The difference is almost significant ($1\ \% < p \leqslant 5\ \%$). The frequency of fathers under Temperance Board supervision is largely the same in both groups (difference 15 ± 10.6).

On the other hand, the child's position among the siblings could not be shown to have any importance in the appearance of nervous manifestations among the subjects.

All the children from families of three or more children, were taken out. Among these, the first-born children, intermediate-born children and last-born children were compared with each other with regard to the frequency of nervous manifestations. The average number of symptoms per case, for first-born boys, was 3.2, for intermediate-born boys 2.5, and for last-born boys 2.6, while, for girls, the corresponding figures were 2.1, 1.8 and 2.7. Mental insufficiency occurred among 25 % of first-born boys, 30 % of intermediate-born boys and 27 % of last-born boys; among the girls, the corresponding figures were 25 %, 18 % and 38 %.

Summary

Nervous manifestations were found in a somewhat higher frequency numerically among only children, than among children from families, both in boys and girls. Abnormality, as judged by the teacher, was seen significantly more often among girls from one-child families than among girls from two-three-child families. The difference for presenting symptoms

TABLE 30. *The frequency of nervous manifestations in the subjects in relation to home conditions.*

Nervous manifestations	Sex	Unbroken homes (U) Total no.		Broken homes (B) Total no.		Difference U–B
Symptoms per case	♂	80	2.6	33	3.4	0
	♀	85	2.7	31	2.7	0
	♂ + ♀	165	2.7	64	3.1	0
Mild mental symptoms on examination	♂	80	40 %	33	27 %	0
	♀	85	34	31	23	0
	♂ + ♀	165	37	64	25	0
Mental insufficiency on examination	♂	80	20 %	33	45 %	–**
	♀	85	29	31	32	0
	♂ + ♀	165	25	64	39	–*
Problem child according to teacher	♂	43	51 %	19	63 %	0
	♀	60	42	18	44	0
	♂ + ♀	103	46	37	54	0

is almost significant. The child's position in the family produces no difference.

Size of the dwelling

The following procedure was adopted, in order to find out if the size of the dwelling was of importance in the development of nervous manifestations among the subjects.

The series was divided up into two groups. The first group comprised those subjects who lived in one room, and the second group, those subjects who lived in more than one room. These two groups were subsequently compared for the frequency of nervous manifestations. The results of this comparison are set out in Table 29.

Several of the children, in dwellings of more than one room, lived in more crowded circumstances than many only children in one-room dwellings. If the degree of overcrowding had been of importance, it would have been justifiable to use a living index as a form of measurement, i.e. to consider the number of room units per family member. The size of the dwelling was classified only as "one room" or "more than one room", because in this investigation, it was considered that the father's disturbing influence on the other members of the family, especially while intoxicated, played a greater part than did the overcrowding itself. Children in one-room dwellings were affected in quite a different way from those in dwellings with more than one room. They had no, or minimal, possibilities of evading the father's presence, since they normally shared even the bedroom with him. Children from homes with more than one room, on the other hand, were able, either alone, or with the mother's help, to keep out of the father's way when he came home drunk.

Table 29 shows that the frequency of nervous manifestations, among the subjects from one-room dwellings, was largely the same as among those from dwellings with more than one room.

Summary

There was no certain difference, concerning the frequency of nervous manifestations, between children living in one-room dwellings and those living in dwellings with more than one room.

Broken home

On dividing up the subjects into those from unbroken and those from broken homes, certain differences could be shown between the two groups where boys were concerned. On the other hand, no similar difference was found with girls (see Table 30).

The average number of presenting symptoms per case, was 2.6 in boys from unbroken homes, and 3.4 in boys from broken homes. The difference is not statistically significant. Mental insufficiency was diagnosed in 20 % of boys from unbroken homes and in 45 % from broken homes. The difference is statistically significant (25 ± 9.8). No definite difference in the frequency of mild mental symptoms on examination, or abnormality in the judgement of the teacher, was found in either group.

The former difference between the groups cannot be explained by other variables in the environment. The age distribution is largely the same among the boys both from broken, and unbroken, homes (4–6 years of age: 33 % and 32 % respectively, 7–9 years of age: 21 % and 30 % respectively and 10–12 years of age: 45 % and 38 % respectively). Similar results were found with regard to the frequency of insufficient mothers (36 % and 32 % respectively), to the frequency of fathers who were under the supervision of the Temperance Board (39 % and 34 % respectively) and to the frequency of only children (12 % and 14 % respectively).

Summary

Mental insufficiency occurred more often among boys from broken homes than from unbroken homes. The difference is significant. This agrees well with earlier findings, when a broken home was found more often among mentally insufficient than among mentally normal boys. The average number of presenting symptoms was also numerically higher among the former than among the latter, but the difference is not statistically significant. No differences were found in the frequency of nervous manifestations in the two groups of girls. As a rule, a broken home means that the father is permanently out of touch with the upbringing of the children. The above result supports the concept of the father's special importance in the personality development of boys.

The mental condition of the paternal grandparents (alcoholism)

In order to determine whether the subjects, whose paternal grandparents were mentally ill or were alcoholics, developed nervous manifestations more easily than the other subjects, the material was divided up into two groups. One group contained subjects with mental illness or alcoholism in the paternal grandparents, while the other contained those with mentally healthy and socially well-adapted paternal grandparents. The two groups were then compared with regard to the frequency of nervous manifestations. Since only isolated cases of mental illness or alcoholism occurred among the maternal grandparents, these were ignored.

TABLE 31. *The frequency of nervous manifestations in the subjects in relation to the incidence of mental illness and alcoholism in the paternal grandparents.*

Nervous manifestations	Sex	Mental illness or alcoholism in the paternal grandparents (M) Total no.		Without mental illness or alcoholism in the paternal grandparents (WM) Total no.		Difference M–WM
Symptoms per case	♂	49	3.0	64	2.7	0
	♀	44	2.8	72	2.7	0
	♂ + ♀	93	2.9	136	2.7	0
Mild mental symptoms on examination	♂	49	43 %	64	31 %	0
	♀	44	30	72	32	0
	♂ + ♀	93	37	136	32	0
Mental insufficiency on examination	♂	49	24 %	64	30 %	0
	♀	44	27	72	32	0
	♂ + ♀	93	26	136	31	0
Problem child according to teacher	♂	23	48 %	39	59 %	0
	♀	29	38	49	45	0
	♂ + ♀	52	42	88	51	0

The results of this comparison are shown in Table 31, which shows that no difference could be demonstrated between the two groups.

Summary

No differences in the frequency of nervous manifestations could be shown between subjects with, and without, mentally ill or alcoholic paternal grandparents.

The state of mental health of the siblings.

Table 32 shows the frequency of nervous manifestations with the material divided up into two groups, one comprising all the subjects whose siblings had nervous symptoms, and the other, all the subjects whose siblings did not have such symptoms. Thirty three only children were not included (11 boys and 22 girls).

It can be seen that significant differences do not exist in the frequency of nervous manifestations between the groups.

Summary

The subjects having siblings with nervous symptoms showed no difference concerning the frequency of nervous manifestations from those whose siblings were free of mental symptoms. This indicates that constitutional factors must be of importance in the appearance of nervous manifestations in the subjects.

Discussion

In the introduction to this chapter, it has already been pointed out that analysing the subject material to determine the importance of isolated factors in the environment, is a difficult procedure from many points of view and the result thereby reached is difficult to interpret. Nevertheless, the main reason why such an analysis has been carried out is that any results

TABLE 32. *The frequency of nervous manifestations in the subjects in relation to the incidence of nervous symptoms in the siblings (33 only children are not included).*

Nervous manifestations	Sex	Nervous siblings (N) Total no.		Mentally healthy siblings (H) Total no.		Difference N–H
Symptoms per case	♂	63	2.7	39	2.8	0
	♀	62	2.6	32	1.9	0
	♂ + ♀	125	2.7	71	2.4	0
Mild mental symptoms on examination	♂	63	41 %	39	21 %	*
	♀	62	31	32	25	0
	♂ + ♀	125	36	71	23	*
Mental insufficiency on examination	♂	63	27 %	39	28 %	0
	♀	62	32	32	25	0
	♂ + ♀	125	30	71	27	0
Problem child according to teacher	♂	38	58 %	22	45 %	0
	♀	39	44	23	22	0
	♂ + ♀	77	51	45	33	*

derived therefrom might be of practical value.

The previous chapter has shown that children from homes with alcoholic fathers present nervous manifestations more often than children from normal homes. Since this is the case, the practising child psychiatrist must ask himself what possibilities there are of helping these mentally damaged children. Alcoholism is widespread in Sweden and many children become ill every year with nervous manifestations because they grow up in an alcoholic environment. Trying to put the alcohol problem to rights, is beyond the compass of the child psychiatrist, but it is most vital that the child psychiatrist should take all possible steps to protect children in alcoholic homes from mental damage. However, in order to do this, he must become aware of the points of attack. He must explore and learn to recognise all the factors in the alcoholic environment, which affect the mental health of the child, not only those that contribute towards producing nervous manifestations, but also those which might strain their already weakened strength.

The author analysed the subject material in this way, in spite of the disadvantages of doing so, in order to develop a continuous plan of action for child psychiatrists, in relation to children from alcoholic environments.

The analysis has shown that three environmental factors were important in relation to the subjects' nervous manifestations, viz., supervision by the Temperance Board, the mother's state of mental health and broken home.

Even if the differences are not large, the children of fathers under the supervision of the Temperance Board, constantly have a lower frequency of nervous manifestations than children of fathers not under such supervision. This applies to both boys and girls. The reason for this is not that Temperance Board-supervised fathers

are especially good fathers. Indeed, their alcoholism, on the average, is as prolonged and difficult to cure as that of the other fathers, while their social adaptability is, if anything, worse. The mothers in these homes are mentally insufficient, as often as they are in the homes where the fathers are not under the supervision of the Temperance Board. Neither can one look for an explanation in the Temperance Board supervised fathers' absence from home more often, and for longer period, than the other fathers, since all the fathers, at the time of the investigation, lived at home, unless there had been a separation, and were under treatment at the Mariapoliklinik. No other conclusion can be drawn from the investigation, except that the supervision itself by the Temperance Board must play a decisive role. In addition, this is supported by the circumstance that children of fathers previously under Temperance Board supervision, but discharged at the time of the investigation, show no difference in the frequency of nervous manifestations, from children of fathers who had never had contact with the Temperance Board.

The next question is: How does this supervision affect the home situation? Those measures taken by the Temperance Board can hardly, in themselves, have had a curative effect on the home environment. As a rule, this has implied only supervision, possibly providing the incentive for the fathers to present themselves for treatment at the Mariapoliklinik. The mothers and children did not receive any kind of supplementary treatment, even in those cases where the Children's Care Committee was called in. Analysis of the material shows that abstinence from alcohol does not play any important part. A possible reason why the children, whose fathers are under Temperance Board supervision, have lower frequencies of nervous manifestations than other children, is that the Temperance Board supervision of the father gives increased security to the mother and child.

Another environmental factor of importance in the frequency of nervous manifestations in the subjects, was mental insufficiency in the mothers. Previously, it has been shown by a number of authors, that mental insufficiency in the mother often causes nervous symptoms among the children, and is stated in the larger text-books as being one of the commonest causes of nervous symptoms in childhood (Kanner 1948, Tramer 1949, Annell 1958, etc.). The German paediatrician v. Harnack (1953) found, in an investigation of 2400 seven-year-old children in Hamburg, that among the environmental factors which could be thought to give rise to nervous symptoms in children, "nervous mother" seemed to play the largest role. In the author's material, this was true of girls but not of boys. Thus in families, where the mother was mentally insufficient, the girls on the average had a higher number of symptoms per case, than girls from homes with mentally healthy mothers. It is difficult to explain why girls only should be affected in the author's series, but this fact possibly supports the idea that girls are more dependent than boys on their mothers for personality development, and so have a greater need of a healthy mother than boys have.

In relation to the environmental factor, "broken home", it appeared instead, that

boys were more sensitive than girls. Thus boys from broken homes were significantly more often mentally insufficient than boys from unbroken homes. No similar difference could be shown between the corresponding groups of girls. In these cases, the mother was always in charge. Those children freed from the disturbing influence of the father would be thought to show a better mental state than those living together with him. That this was not so in relation to boys, supports the idea that boys depend on the father's presence in the home, to a higher degree than do girls, for satisfactory personality development.

Could not the results of the analysis obtained, produce practical measures designed to create a more favourable environment for these children? There is reason to expect that this is possible. Regular and prolonged control of the father by the Temperance Board, supporting measures especially directed towards the mentally insufficient mother and in those cases of separation, psychotherapy for the children and especially for the boys, should in conjunction, certainly lower the frequency of nervous manifestations among these children.

CONCLUSIONS

The chronic alcoholic often supports his family badly. In spite of this the material standard of the home is usually normal because the wife contributes financially by going out to work. Emotional disturbances are common in the home. Every third marriage ends in divorce, and every third wife is mentally insufficient, only exceptionally seeking help for this.

The children show signs of physical and mental neglect, more often than children from average homes. There are usually nervous symptoms of different kinds and difficulties of adaptation with companions and in school. The possibilities of help, which society offers, in the form of free examination and treatment at child welfare centres and child-guidance clinics, are not used to the same extent by these children, as by other children, in relation to the need. Instead, they look for help to the ordinary out-patient departments and hospitals, for different kinds of psychogenic physical symptoms, which often demand examinations and investigations which are prolonged and costly to society. Co-operation from the parents is usually poor.

In spite of the dire consequences for the rest of the family, the fathers' alcoholism is most often kept secret. It is seldom that this is known to the Children's Care Committee, child welfare centre or the doctor in charge of the case. The father's alcoholism was not always detected even in cases which were being investigated and examined at the child-guidance clinic over many years. It is quite obvious that the connection between the father's alcoholism and the nervous symptoms of the child was clear to the parents in these cases.

Those children get on best, whose fathers are under the supervision of the Temperance Board. Although this is the case, it is only seldom that the Temperance Board takes direct measures in helping to support the child. In only a few cases of alcoholic fathers, did the Temperance Board report this fact to the Children's Care Committee.

Thus the children of alcoholics are especially in need of help. Because of the parents, they are not given the opportunity of receiving any help. Those measures which society can take and which can be shown to provide a certain amount of help are not used to the full either. It is in the interests of society to realise that the effects of alcoholism stretch much further than the damage which the alcoholic brings upon himself. It is necessary that the other members of the family are considered when measures for helping the alcoholic are under discussion. A first step in the right direction would be a more intimate co-operation between the different social welfare services than exists at present.

GENERAL SUMMARY

Chapter 1

On the basis of earlier investigations by the author, the hypothesis is put forward, that children who grow up in homes which are severely disturbed emotionally, often develop nervous manifestations which can take the form of physical symptoms. Because of this, such children are often examined at hospitals for physical diseases, and come, either late or not at all, for child psychiatric investigation and treatment. This hypothesis is tested on children of male chronic alcoholics.

The following section gives a brief history and guide to temperance legislation and alcohol habits in Sweden. Every community in the country has a Temperance Board whose duty it is to maintain temperance and help to rehabilitate those suffering from alcoholism. In those cases where this board becomes aware that children are exposed to distress or neglect as a result of the alcoholism of the parents, it is the duty of this board to communicate the fact to a Children's Care Committee which should be found in every community. The Children's Care Committee must then take the necessary steps to protect the children.

Earlier investigations in the field are referred to briefly. In spite of the fact that a number of child psychiatric investigations have shown that the frequency of alcoholic fathers is high among children with behaviour disorders, no previous modern child psychiatric investigation exists, carried out on children of chronic alcoholics.

Chapter 2

The principles used in the choice of subject material are discussed. It is pointed out that it is difficult to get children from homes which are representative of chronic alcoholics in Stockholm, if at the same time a certain degree of severity of alcoholism is required. The author chose a subject material where the father's alcoholism was prolonged and well documented, despite the fact that, taken this way, the material was not representative of the population of the City of Stockholm, from the point of view of e.g. social groups.

The subjects were chosen from among the children of male patients attending an out-patient department for alcoholics of the City of Stockholm Temperance Board, the Mariapoliklinik. Only children aged 4–12 years were included in the investigation material. Children in these age groups were found in a total of 170 families during the time that the investigation was being made. In five of these families the children had been in foster homes for several years, and were therefore not included in the series. As a result, the latter comprised 261 children from 165 families. Fifteen per cent of the subjects' families refused to co-operate in the investigation. From the social point of view, these fa mi-

lies constituted a negative selection. Over half of the children who went to school were designated as problem children by the teachers. Thus, 229 children from 141 families were investigated.

The controls were chosen with the help of the records of the school and the child welfare centre on the "social twin" principle. Those subject, who were on the census register of the City of Stockholm, received a control of the same age and sex, whose father had the same or similar job as that of the subject's father. The subjects who attended school received controls from their own class. An attempt was made to match subjects with controls whose school work was of similar standard. Children not in school were given controls from the child welfare centre attended by the subjects. In this way, 187 controls were chosen in all. Of these, 17 cases (9 % of the total) were excluded because their fathers were known to the Temperance Board as alcoholics. In this way the control series comprised 170 cases. Five control families refused to cooperate and two moved from Stockholm after the material was selected and it was not possible to trace them again. Thus 163 children from as many families were included in the investigation.

The majority of cases were examined at Kronprinsessan Lovisas Barnsjukhus, but in a number of cases the examination was performed at home for various reasons. It was uncommon for the mother not to follow the child to the examination.

The examination comprised an interview with the mother concerning the mental and physical state of health of the child according to a standardised questionnaire, together with a physical and mental examination of the child. An objective history was obtained in the majority of cases. The opinion of the teacher was obtained about all the school children. In those cases where the children had attended the child welfare centre the case histories were studied. If the children had visited a doctor or been in hospital the case histories were requested, or direct contact with the doctor in question was made in order to obtain the information required. Home visits were made in a number of cases in order to complete the history. Finally, the records of the Children's Care Committee and the child-guidance clinic were checked as to whether the children were known there or had been patients there. If such was found to be the case, information was obtained from the case histories kept by these organisations. Information on the father's alcoholism, mental condition and social adaptability was obtained from the special case histories supplied by the doctors of the Mariapoliklinik for this investigation.

When all the historical data had been assembled an attempt was made to assess their reliability. This seemed to be good except that information given by the mothers about the father's alcoholism. This information was often unreliable.

Finally, an account is given of the statistical methods used in the investigation.

Chapter 3

The subjects consisted of 229 cases (113 boys and 116 girls) and the controls of 163 cases (83 boys and 80 girls). The distribution of the different sex and age groups was largely the same in both series.

The distribution of social groups among the subjects was not representative of the population of the City of Stockholm, since social group III is overrepresented (83 % of the subjects belong to social group III). There was a good agreement regarding the father's job between the subject and the control series.

It was stated that alcoholism occurred among the grandfathers in 33 % of cases, while among paternal grandmothers and maternal grandparents it occurred only occasionally.

As a rule, alcoholism in the subjects' fathers, had been prolonged and brought about social complications. Thus in 44 % of cases the fathers had been alcoholics for more than ten years, and in 63 % of cases they appeared drunk almost every day, while in 53 % of cases their intoxication could be described as severely disturbing. Sixty nine per cent of cases had been reported to the Temperance Board because of alcoholism, 12 % had been in an alcoholic institution, 20 % had been convicted and 16 % were incapable of supporting their families. Mental deterioration was seen in 21 % of the fathers. Alcoholism was stated never to occur among the controls' fathers, while 9 % had had mild mental insufficiency requiring medical care.

Thirty two per cent of the subjects' mothers and 10 % of the controls' mothers were judged to be mentally insufficient at the time of the investigation. The difference is statistically significant. The commonest symptom-picture among the subjects' mothers was "worn-out mother" and depression. Two of the subjects' mothers were alcoholics, but none were found among the controls' mothers. While ten of the controls' mothers, i.e. over half of the mentally insufficient had been to the doctor for their mental difficulties, only one of the subjects' mothers had taken this course of action.

The frequency of mothers in employment was higher among the subjects than among the controls (52 % and 36 % respectively). Of these, 23 % of both series worked half-time, while 29 % of the subjects' mothers and 12 % of the controls' mothers worked full-time. This last difference is highly significant.

The average number of children in the subjects' families was 2.3, and in the controls' families 2.4. In the subjects' series there were often several children from the same family, which was not the case in the controls' series. The subjects, therefore, were, on the average, drawn from larger families than were the controls. The distinction is insignificant, however.

Divorce or separation had taken place in 28 % of the subjects' marriages and 4 % of the controls'. The difference is highly significant. In one subject's family the parents lived together unmarried, but in the controls, all the parents were married. The home conditions in all the subjects' families were described as severely disturbed. The conditions in the dwelling and the material standard in the home were, however, with few exceptions, good in both series.

Ten per cent of the subjects were born outside marriage which largely corresponds to the frequency of illegitimately born children in Stockholm for the year 1957. Only 1 % of the controls was born outside marriage. In 48 % of the subjects' families the mother had been pregnant at the time of marriage, but this was so in

only 25 % of the controls' families. The difference is highly significant.

Complications in pregnancy were found in only a few cases of each series.

No differences could be shown concerning the frequency of labour complications (premature birth, forceps delivery, breech delivery and foetal asphyxia) and delayed development. Breast feeding (3 months or more) was, on the other hand, more common in the control than in the subject series. The difference is significant. Prolonged and difficult vomiting in infancy had occurred significantly more often among the subjects than among the controls.

Prolonged physical illness, or physical illness which required medical treatment, occurred in 11 % of the subjects and 21 % of the controls. The difference is significant.

In spite of this, as many subjects as controls had visited the out-patient department complaining of physical symptoms, i.e. 24 % of the subjects and 19 % of the controls. However, definite physical illness could be shown in only about one quarter of the subjects, but this occurred in two thirds of the controls. The others, 18 % of the subjects and 6 % of the controls, had complained of symptoms which were probably mentally conditioned or influenced. The difference is highly significant.

Thirty four per cent of the subjects and 27 % of the controls had been in hospital with physical symptoms. An organic aetiology was confirmed in about two thirds of the subjects and in about six seventh of the controls. The remainder, 10 % of the subjects and 4 % of the controls, had had physical symptoms which were probably psychogenic in origin or psychogenically influenced. The difference is almost significant.

Six per cent of the subjects and 5 % of the controls had attended the child-guidance clinic with mental disorders. Throughout, co-operation from the subjects' parents had been poor, and in the majority of cases, the treatment of the children had been broken off by the parents before the doctors considered it to be complete. In about one half of the cases the father's alcoholism had been unknown throughout the whole treatment period.

Of the 141 subjects who were of school age, 134 were in a normal class, three in a class for retarded children two in a "reading" class and one in an "observation" class. This implies that the frequency of subjects in special classes is no higher than among Stockholm children in general.

The frequency of visits to the child welfare centre was low among the subjects. Only 51 % of cases had, at any time, been examined there. During the last few years, about 90 % of all newborn children in Stockholm have been examined at the child welfare centre.

The Children's Care Committee, had been informed of the father's alcoholism in 13 % of cases. Only in one case had this caused them definitely to separate the child from the home. All the controls were unknown to the Children's Care Committee.

Examination of the children revealed the following:

With few exceptions, the general state of health was good in both series. Pathological findings on examination were seen in 8 % of both subjects and controls.

Developmental abnormalities occurred in isolated cases of both series. Physical puberty had appeared in a few of the girls in both series. The frequency of caries was largely the same in both subjects and controls, but 39 % of the subjects and 21 % of the controls had teeth which needed filling. The difference is significant.

At the time of the investigation, the average number of presenting symptoms per case was 2.8 for boy subjects and 2.7 for girl subjects, while for the controls the corresponding figures were 0.6 for boys and 0.8 for girls. The difference is highly significant. Certain sex differences could be shown in relation to the presenting symptoms. Encopresis occurred only in boys, while diffuse abdominal pain of psychogenic origin, appeared significantly more often among girls than among boys. All the 24 recorded symptoms appeared more often numerically among subjects than among controls. A statistically significant difference was found with ten symptoms.

Mental insufficiency was shown in 29 % of the subjects and in 5 % of the controls, while mild mental symptoms on examination occurred in 34 % of the subjects and 18 % of the controls. The differences are highly significant and almost significant respectively. The other subjects were mentally normal. The kinds of mental insufficiency in the subjects were mainly of anxiety neuroses and depressions.

About 5 % of both subjects and controls were judged as intellectually retarded (corresponding to feeble-mindedness or worse). Of these, two subjects were imbeciles. Among the controls there was no imbecility.

The teachers had assessed 48 % of the subjects and 10 % of the controls as being problem children. The difference is highly significant.

Finally, the results of the various judgements of mental condition are compared. It is seen that the teachers more often judge the younger boys (7–9 years) to be problem children than the older boys and all the girls, despite the fact that the frequency of mental insufficiency is the same in all groups. The cause of this discrepancy in judgement depends on the fact that the symptoms of the younger boys are more striking and disturbing in the school class than are those of the other children. A number of cases of prolonged and for the child, debilitating neuroses, have been overlooked by the teachers.

Finally, the results are discussed.

Chapter 4

The subjects are analysed in this chapter in order to clarify the importance of certain individual environmental factors in the development of nervous manifestations among the subjects.

The average number of presenting symptoms per case was lowest in the age group 4–6 years, being similar in boys and girls, and highest in the age group 10–12 years, but more pronounced in girls. There were no statistically significant differences. Mental insufficiency occurred to the same extent in all the age groups, in both boys and girls. According to the teachers' judgements, the highest frequency of abnormality was found among the younger, 7–9-year-old boys, i.e. 74 % of the total.

No differences concerning the frequency of nervous manifestations could be shown between the three social groups.

The subjects' constitutional type (asthenic as opposed to the others) and bodybuild (underweight, normalweight and overweight) could not be shown to have any decisive importance with regard to the frequency of nervous manifestations.

No difference could be shown in the frequency of mental symptoms among the subjects with and without a history of brain damage.

It could not be shown that the type of alcoholism in the father, or his way of reacting towards it, had any decisive effect on the mental health of the child.

However, those subjects who had fathers under Temperance Board supervision did not show nervous manifestations as often as those whose fathers had not had contact with the Temperance Board, or as often as those whose fathers had earlier been under supervision but had been discharged. Since other environmental factors could not be shown to have any importance in this connection, it would seem that the child's situation in the family is favourably influenced by the father's contact with the Temperance Board. This is so, in spite of the fact that among the fathers under Temperance Board supervision, a high frequency of severely disturbing intoxication exists, together with an inability to support the family.

In the homes where the mother was judged to be mentally insufficient, the girls, on the average, had a higher frequency of presenting symptoms per case, than girls from homes where the mother was judged as mentally healthy. The difference was statistically significant. The frequency of other nervous manifestations, was numerically higher among girls with mentally insufficient mothers, than among those with healthy mothers. However, these differences were not statistically significant. Similar differences could not be shown among the boys.

Girls from homes where the mother had half-time employment, were not mentally insufficient as often as those whose mothers were not employed outside the home.

Throughout, only children had nervous manifestations numerically more often than children from families with four children or more. The average number of presenting symptoms per case was almost significantly higher among the former than among the latter. Abnormality according to the judgement of the teachers occurred significantly more often among girls from one-child families than among girls from two-three-child families. The child's position among the siblings, on the other hand, did not seem to be of any importance.

Mental insufficiency appeared significantly more often among boys from broken homes than among boys from unbroken homes. On the other hand, the remaining nervous manifestations occurred equally often among the former as among the latter. The frequency of mental insufficiency among the girls was also the same in both groups.

Finally, the results of the clinical analysis are discussed. The results obtained lead one to pose the question whether or not regular and prolonged supervision of the father by the Temperance Board, supporting measures for the mentally insufficient mother and possibly also treatment of the children, could reduce the frequency of nervous manifestations among these children.

PART TWO

Children in the Psychiatric Department of Kronprinsessan Lovisas barnsjukhus between the years 1953–58, whose fathers were chronic alcoholics

The case histories of the patients in Part II, are available at the Department of Psychiatry, Kronprinsessan Lovisas barnsjukhus

CHAPTER 5

MATERIAL

Introduction

In Part I, it was seen that children from homes where the father was a chronic alcoholic, had nervous symptoms of different kinds more often than children from homes in which alcoholism did not exist. In spite of this, the frequency of children coming to the child psychiatrist for treatment does not differ in the two groups. Only a small proportion of the mentally disturbed children from homes where the father was an alcoholic came to the child psychiatric department for investigation and treatment. In those cases where children of chronic alcoholics sought medical advice, they came most often to ordinary hospitals or to general practitioners.

In spite of this, every year a certain number of children of chronic alcoholics are admitted and treated in child psychiatric departments.

In Part II, which consists of a retrospective investigation, a series of patients from the Psychiatric Department at K. L.B. in Stockholm will be analysed. The questions which need to be answered are those previously set out:

1. What is the clinical importance of alcoholism in the father?

2. Which children of alcoholic fathers are admitted to child psychiatric departments?

The Psychiatric Department at K.L.B. was opened on the first of May 1953. There were places for 12 children up to 16 years of age. On the first of November 1957 another ward of eight beds was opened, for boys from 13–21 years of age. By reducing the demands made it was possible to admit girls up to 21 years of age into the larger ward. An account of the admissions to the larger ward during the first four years has been given by Ahnsjö (1958). The wards chiefly take children from the City of Stockholm, but a number of places are reserved for children from the County of Stockholm. Only in exceptional cases are children taken from other parts of the country.

All the children admitted to the clinic undergo a careful clinical investigation, involving an inquiry into the social background together with complete physical and mental examinations.

The Material and its Selection

The material for the retrospective investigation was selected from the 645 cases, admitted to the clinic between 1.5.53. and 1.5.58. The case-histories of all these patients were studied, and those cases, where there was a history of chronic alcoholism in the father, were taken out, but only when the father's alcoholism was described as disturbing to the family.

By this means, a material was obtained comprising 102 cases.

With the experience gained in Part I, the Temperance Board of the City of

TABLE 33. *Admissions to the Psychiatric Clinic 1953–58.*

Year	Number of cases admitted to the Clinic	Those with chronic alcoholic fathers	
		No.	%
1953 (1/5–31/12)	72	11	15
1954	113	18	16
1955	136	28	21
1956	123	20	16
1957	144	27	19
1958 (1/1–30/4)	57	17	30
Total	645	121	19

TABLE 34. *The Clinic material grouped according to age and sex.*

Sex	Age in years											
	—4	4	5	6	7	8	9	10	11	12	13 –	Total
Boys	5	3	1	5	6	8	6	9	5	8	27	83
Girls	1	1	0	2	3	1	4	2	2	1	21	38
Total	6	4	1	7	9	9	10	11	7	9	48	121

Stockholm was contacted, where despite the absence of information in the case-histories, it was thought that alcoholism might exist. In the board's records, the fathers of the 441 Stockholm children, were checked. As a result of this, a further 19 cases of alcoholism among the fathers were found, in addition to the 102 cases known to us, mentioned above, of whom 94 were registered in the City of Stockholm. In this way the material came to comprise 121 cases.

In Table 33, the material is grouped according to the various years of admission. It can be seen that about one case in five, admitted to the clinic had a father who was alcoholic. If the frequency for different years is compared, it is seen that the frequency was numerically twice as high in 1958 as in 1953. However, the difference is not significant (15 ± 7.7). According to Österlund (1957) etc., the end of rationing of alcohol in 1955 was followed by a rise in alcoholism in Sweden.

Sex and age distribution in the material are shown in Table 34. The number of boys is at least twice as high as the number of girls. The girls do not predominate in one single age group, but after puberty the proportion of girls rises steeply. About 40 % of all the cases were found to be thirteen years of age or more, i.e. older than the subjects in the investigation material of Part I.

The distribution into social groups is set out in Table 35. As with the subjects in Part I there was a heavy preponderance of social group III in this material.

Details of the Fathers' Alcoholism

Of the 121 fathers, 94 were census registered in the City of Stockholm. Sixty

TABLE 35. *Social grouping of the Clinic material in relation to that of voters in the City of Stockholm at the 1956 election.*

Social group	Patients		Voters	
	Boys	Girls	Men	Women
I	1 (1 %)	2 (5 %)	32,676 (13 %)	29,250 (10 %)
II	17 (20 %)	5 (13 %)	100,382 (40 %)	152,102 (50 %)
III	65 (78 %)	31 (82 %)	116,314 (47 %)	122,178 (40 %)

nine per cent of these were known to be alcoholics by the Temperance Board. There was a history of alcoholism in 75 of the cases registered in the City of Stockholm, i.e. in about 80 %. On the other hand, there was no history of alcoholism in 19 cases or about 20 % of the fathers in spite of the fact that they were known to be alcoholic by the Temperance Board. A summary of the information concerning these latter fathers and their home circumstances, is set out below.

Case 17/53: A six-year-old boy with a speech disorder. Father "calmer than the mother, plays more with the children. Commands a certain respect, e.g. can make them obey him by looking sharply at them." He was described by the doctor in charge as "typically calm, respectable normal worker, who seems to have understanding ...". Nothing of note said about the home circumstances otherwise.

Case 30/53: Nine-year-old boy with retarded development. Father and home conditions described only as "normal".

Case 13/54: Ten-year-old boy with temper tantrums. Parents separated since 1951. Father and home conditions described as "abnormal". Father regularly visits the home, often drunk, but alcoholism as such denied.

Case 42/54: Six-year-old boy with retarded development. Separation 1953. Father described as "very nervous and uneasy, appears troubled, sometimes gets attacks of weeping, wanted to take his own life".

Case 80/54: Three-year-old boy with depression. Concerning the father, it is noted that he is "considerably more gentle and natural than the mother, who appears to be very hard and lacking in understanding towards the boy. She has no real love for the boy".

Case 88/54: Seven-year-old girl with neurological and mental symptoms. Father noted as "mentally healthy", home conditions stated as normal.

Case 112/54: Fifteen-year-old boy with adaptation difficulties in school. Separation 1941. Father has custody of the boy. Father described as "able" but "has great difficulty in accepting that the boy has mental problems or, if he has such problems, that they can be the cause of his being kept in hospital". Says "the boy has been beaten rather a lot"—"On the whole the father made a good impression."

Case 130/55: Two-year-old boy with retarded development. Father described as "calm and sensible, doing his own work and helping in the home. He is very fond of all the children, devoting a lot of time to them". Home conditions stated to be essentially normal.

Case 88/56: Ten-year-old boy who ran away from home. There is no evidence of abnormality in the father or disturbance in the home.

Case 99/56: Seven-year-old boy who ran away from home. The case history reads: "Father seems emotionally very rigid and had obviously little understanding of the boy. Often uses corporal punishment. Mother is epileptic." No information about alcoholism in the home.

Case 115/56: Eight-year-old boy with headache. "Mother says that the father is very kind" but he has "previously been troubled by a migrainous headache, he is sensitive and easily upset". In addition the case history reads "The present home conditions appear to be harmonious."

Case 141/56: Six-year-old boy with hysterical outbursts. Father and the home conditions described as normal.

Case 51/57: Fifteen-year-old boy with anxiety. Father described as "a fat pyknic, open, easily approachable with what appears to be a stable and sensible attitude towards life". The home conditions were reported as being good. After discharge from the clinic, the patient was put into a foster home, and the foster mother later reported that she "did not understand what was wrong with the home and wonders if it could be alcoholism ... but I (the doctor in charge) maintain that our idea is quite different ...".

Case 132/57: Eight-year-old boy with aggressive outbursts. Father described by the mother in the following way: "In recent years he has become more and more nervous." This was while he was being questioned about the boy's adaptation difficulties. Father is said not to be an alcoholic. The case history concludes: "The differences between the parents depend on the fact that they are quite different types and that the father shows no interest in the home".

Case 157/57: Fourteen-year-old boy who stole. Father stated to be "strict, quick to smack them but looks after the children. ... While the mother is out working in the evenings, the father sees to the children and puts them to bed."

Case 14/58: Twelve-year-old boy with difficulties in school. Separation 1956. Father described as "nervous" but alcoholism denied.

Case 26/58: Sixteen-year-old girl who stole, and appeared to be sexually unstable. Had repeated hysterical attacks. Father described as "healthy and young-looking, sometimes drinks". The home conditions stated to be normal.

Case 34/58: Nine-year-old boy with extreme motor restlessness. "The parents seem to be bohemian and rather odd." Father is sometimes away travelling, which the patient thinks is very upleasant. He is attached to the father. Does not react so strongly if the mother goes away. The home conditions described as being fundamentally normal.

Case 66/58: Fifteen-year-old boy with aggressive outbursts. Father stated to have been convicted for embezzlement and burglary, but alcoholism denied. Mother lives alone with the patient, but the home conditions are otherwise stated to be normal.

All the above-mentioned fathers were alcoholics at the time the children were admitted to the clinic.

In several of these cases it is certain that there were disturbances in the home, but alcoholism was never mentioned in relation to them. Even in those cases where the parents were separated, the mother concealed the father's alcoholism, in spite of the fact that in every case this had existed while the parents were living together. In a number of the cases, the doctor had had repeated contact with the alcoholic father, without the latter having mentioned the alcohol problem. In one case, even an outsider suggested that the father was an alcoholic, but this was dismissed by the doctor in charge who thought that this could not be so.

While the father's mental insufficiency, expressing itself in alcoholism passed unnoticed in these cases, it was stated in a number of them that the mother's nervousness had been the predominant factor in the development of nervous symptoms and adaptation difficulties in the children.

Sixty seven of the homes were broken, i.e. 55 % of the families were separated. In every case except one, the mother had the custody of the children. In case 112/54 the child was in the care of the father.

Summary and Discussion

If the subject material of Part I is compared with the clinic material, certain differences appear between the two series.

While the frequency of nervous manifestations was the same among both boys and girls in the former series, there were twice as many boys as girls in the latter series. The subject material in Part I comprised only children between four and twelve years of age, while 40 % of cases in the clinic material were over twelve years and 5 % were under four years. However, the sex distribution among the children over twelve years was largely equal. Thus, the different distribution of the sexes in both series could not be explained by a difference in age distribution.

The difference could depend on the relative infrequency of more severe psychopathological symptoms in the subject series with a predominance in the clinic series, and a more frequent appearance among boys than girls. However, this can hardly be the case. Severe mental symptoms were found relatively often in the subject series in Part I, and to the same extent in both boys and girls.

The probable explanation of the sex difference in the clinic material is presumably that the boys show a symptom picture different from that of the girls, and one which is more disturbing to the environment. This was shown approximately, on analysis of the subject material in Part I. Among the boys there, the frequency of symptoms such as encopresis, motor restlessness, speech disorders, etc. was numerically higher than among girls. On the other hand, among the girls, the frequency of physical symptoms of psychogenic origin, depression, etc. was comparably higher than among the boys. The former symptoms can be assumed to be more disturbing socially than the latter. Similarly, the teachers stated that boys were more often problem children than were girls, in spite of the fact that the frequency of mental insufficiency was the same among boys as among girls.

It was not possible to make any comparison between the types of alcoholism of the fathers of both series, since knowledge of the fathers' alcoholism in the clinic material is extremely limited. However, the frequency of cases, who were known to the Temperance Board as alcoholics, was the same in both series.

Finally, with regard to the position at home, the frequency of broken homes was seen to be twice as high in the clinic material as in the subject material from Part I. Thus, a separation in these families did not always imply an improvement in the home situation from the children's point ot view. In point of fact, the contrary was true. This agrees well with the findings from the analysis of the subject material in Part I.

It has often appeared from the case-histories in Part I that the mother wanted divorce but did not dare to start proceedings because of the father. At the same time, it has also appeared that the father often refuses to allow the child to be treated, or even breaks off treatment which is already under way. It is therefore likely that those mothers who are divorced, to a larger extent than those still married to an alcoholic, seek the advice of a child psychiatrist.

CHAPTER 6

MAIN REASONS FOR ADMISSION

All the cases were referred by a doctor. The school doctor had taken the initiative in 37 cases (28 boys and 9 girls) or in 31 % of the total. In 36 cases (26 boys and 10 girls) or 30 % of the total, it was the Children's Care Committee's doctor who was responsible. "The other doctors", i.e. in the majority of cases the doctors at the child-guidance clinics in the City and County of Stockholm had referred 21 cases (12 boys and 9 girls) or 17 % of the total. The remainder, 27 cases (17 boys and 10 girls) 22 % of the total, were admitted through the hospital's own child-guidance clinic.

The main causes of admission are set out in Table 36. A number of cases have been registered twice as it was sometimes difficult to decide what had been the most important reason for admission. It is seen from the table that more than one half of the school children had considerable adaptation difficulties in school, and that about one third had pronounced social adaptation difficulties outside school.

Social Adaptation Difficulties (in school)

A total of 53 cases (36 boys and 17 girls) had had considerable adaptation difficulties in school.

In 17 of 103 schoolchildren, or in 17 % of the total, the adaptation difficulties were caused by low intellect (11 boys and 6 girls) (cases 30/53, 84/53, 86/53, 4/54, 38/54, 42/54, 11/55, 58/55, 103/55, 129/55, 153/55, 12/56, 108/56, 138/56, 24/57, 100/57 and 143/57). Nine of these (5 boys and 4 girls) were found feeble-minded. There were seven imbeciles (5 boys and 2 girls). Idiocy was found in one case (a boy).

In the other 36 (25 boys and 11 girls) adaptation difficulties occurred in school in spite of normal abilities.

The commonest symptom in these cases was truancy or refusal to attend school. This was found in 18 cases (10 boys and 8 girls), 17 % of the total number of schoolchildren (cases 80/53, 2/54, 7/55, 49/55, 57/55, 115/55, 116/55, 142/56, 25/57, 31/

TABLE 36. *Main reasons for admittance to the Clinic.*

Main reasons for admittance	Boys	Girls	Total No.	Total %
Social adaptation difficulties (in school)	36	17	53	51[1]
Social adaptation difficulties (other)	30	7	37	31
Symptoms of mental insufficiency	49	31	80	66
Developmental retardation	11	5	16	13

[1] Estimated on 103 children who went to school.

57, 41/57, 85/57, 111/57, 149/57, 165/57, 43/58, 45/58 and 52/58). This symptom was almost evenly distributed among the different age groups.

Pronounced difficulties in concentration were the main problem for ten cases, all boys (cases 78/53, 102/54, 114/54, 25/55, 66/55, 31/56, 115/56, 134/56, 9/58 and 66/58).

In three cases, all boys (cases 134/55, 159/57 and 49/58), the main reason given was aggressiveness towards the teacher and the class companions. Well-marked difficulties with companions were mentioned in two cases (1 boy and 1 girl) (cases 81/55 and 60/57), and motor restlessness in one boy (case 34/58). One girl had elective mutism (case 33/55). Finally, one girl (case 51/56), was such a nuisance during the lessons that it was necessary for her to stop attending school.

Social Adaptation Difficulties (other)

Six (5 boys and 1 girl) of the 37 patients (30 boys and 7 girls), who had social adaptation difficulties outside school, were retarded in their intellectual development (I.Q. less than 85) (cases 36/54, 58/55, 88/56, 108/56, 24/57 and 20/58).

Nine patients (7 boys and 2 girls) had been guilty of simple pilfering (cases 36/54, 58/55, 146/55, 108/56, 16/57, 149/57, 163/57, 20/58 and 42/58). Four of these were intellectually retarded.

In five cases, all boys (cases 44/53, 71/53, 4/56, 31/56 and 157/57), there had been more serious and regular pilfering or stealing, together with simple housebreaking. The following is an example:

Case 4/56: 11-year-old boy, who during the last six months had often been left alone, because his mother had been employed away from home. Has burgled shops and kiosks 29 times in the last few months. Came with kr. 100 notes to school and divided up the money among his companions. Several times caught in the act by the police. Impossible to make him aware of his guilt or to persuade him to stop stealing.

Eleven children (10 boys and 1 girl) had run away, including one intellectually retarded boy. A summary of all the cases appears below:

Case 112/54: 13-year-old boy. "For the past year, violent, uneasy, runs away aimlessy."

Case 116/55: Ten-year-old boy. Since 4–5 years of age has had a tendency to run away from home. Finally, intensive vagrancy.

Case 88/56: Ten-year-old boy. For the last six months mentally changed, often has fits of rage and tries to run away. On one occasion walked 20 kilometres. Mentally retarded.

Case 99/56: Seven-year-old boy. For the last year often ran away. Set off from home in the morning, then roamed around town without food or supervision the whole day.

Case 144/56: 13-year-old girl. "... as soon as she comes home (from school) she goes out, roaming around town or in the suburbs".

Case 25/57: 13-year-old boy. For about a year vigorous vagrancy, often together with pilfering.

Case 41/57: 14-year-old boy. During the previous months joined a gang in the neighbourhood, and in this time "was out of the house almost every hour of the day".

Case 132/57: Eight-year-old boy, who had been about alone in the last years, drifting aimlessly through the town.

Case 144/57: Five-year-old boy. Got up early in the morning before the rest of the family was awake, and went out into the streets alone, where he drifted about.

Case 3/58: Six-year-old boy. Recently began to run away, "needs to be supervised constantly".

Case 66/58: 13-year-old boy. Excluded

from school for 14 days. "Drifted about town, attracted towards gangster types."

Sexual symptoms had occurred in six cases (3 boys and 3 girls).

In three cases (girls) it had taken the form of sexual instability, the first one in conjunction with vagrancy, the second with pilfering and the third with suspected alcoholism.

Case 115/55: 13-year-old girl who, according to what she said herself, had had intercourse with boys from the age of nine. From 9–10 years of age had regular intercourse with boys and had been isolated from girl companions of the same age. Sought after by police who found her in sport-huts etc., sometimes together with a number of older men. When she came home she was tired, filthy dirty and depressed. Otherwise no asocial features.

Case 85/57: 15-year-old girl who hung around the boats in the town habour, often truanted from shool during the last term. Said she had been drunk on a number of occasions. Stated that she had "been raped" many times. At the Children's Care Committee, where she was well known, she was considered to be "advanced".

Case 26/58: 16-year-old girl who had begun to "go out at nights" for some months. Also pilfered and was suspected of being an alcoholic.

Two boys were exhibitionists, and one of them was mentally retarded.

Case 24/57: 14-year-old boy. During stay at the children's home often exposed himself to his companions. Intellectually feebleminded.

Case 139/57: 17-year-old boy, who since the age of ten years on several occasions masturbated in public, once in front of the whole class and school-mistress while a lesson was in progress.

One boy was known to have made a serious attempt at rape.

Case 60/58: 13-year-old boy. According to the foster mother, he attacked her and made a serious attempt at rape, as a result of which she was injured. Previously, on several occasions, threatened to kill her and thereby tried to force her to have intercourse.

There were two cases of addiction. In one case the substance was alcohol and in the other, "thinner".

Case 38/56: 13-year-old girl, who allied herself to "the worst trash in the neighbourhood and hung around low dives. Repeatedly appeared drunk in public".

Case 153/57: 13-year-old boy. For some months severely addicted to "thinner" which he inhales. Intoxicated for the greater part of the day. Says he is unable to give up his addiction.

One boy (case 134/55) made repeated aggressive attacks on his companions, while another (case 169/57), had prolonged and severe incapacity for work and lay at home without the slightest inclination to work, despite the fact that he was physically healthy. Finally, one boy (case 126/57), was said to have started a fire on the kitchen floor. However, it was stated that this had only happened on one occasion.

Symptoms of Mental Insufficiency

A total of 80 patients had been admitted to the Department (49 boys and 31 girls) mainly because of symptoms of mental insufficiency. In the following these symptoms are divided up into "non-physical symptoms" and "physical symptoms". By non-physical symptoms is meant such symptoms as irritability, emotional instability, motor restlessness, depression etc., and also symptoms such

TABLE 37. *Symptoms of mental insufficiency among patients in the Clinic material.*

Clinical picture dominated by	Boys		Girls		Total	
	No.	%	No.	%	No.	%
Non-physical symptoms	31	37	12	32	43	36
Physical symptoms	12	14	17	45	29	24
Atypical symptom picture	6	7	2	5	8	6
Total	49	—	31	—	80	—

as enuresis and encopresis when these are psychogenic in origin. A number of cases with difficulty in social adaptation were included in this group. Among the physical symptoms were diffuse abdominal pain, headache, giddiness, astasia-abasia, etc., i.e. symptoms which are not usually thought in the first place as having a psychogenic aetiology.

In Table 37, the symptoms of mental insufficiency are divided up in this way. It can be seen from the table that the boys have mainly non-physical symptoms, while the girls have mainly physical symptoms. Non-physical symptoms appeared as often among boys as among girls, i.e., in 37 % and 32 %, respectively. On the other hand, physical symptoms were more common among girls (45 %) than among boys (14 %). The difference is highly significant (31 ± 8.9).

Seven of the 29 patients with physical symptom of psychogenic origin (3 boys and 4 girls), were intellectually retarded, i.e. had an I.Q. of less than 85. Their symptoms are summarised below:

Case 11/55: 16-year-old girl with an I.Q. on the Terman-Merrill scale of 80. "Can develop fits of rage when she screams, kicks and fights. After such an outburst she is completely exhausted, white about the lips and feeling sick." Neurological condition, including EEG, normal.

Case 94/55: Four-year-old boy, intellectually on the border between imbecility and idiocy. Admitted acutely as for the previous four days he had been very restless at home, screaming almost without pause. On admission "the brain is affected". Because of suspected encephalitis transferred to the Medical Department where he was investigated and shown to be neurologically normal.

Case 103/55: 14-year-old boy with an I.Q. on the Terman-Merrill scale of 79. For the past year constant headache sometimes with vomiting. Neurological condition including EEG, normal.

Case 21/56: 9-year-old girl with an I.Q. on the Terman-Merrill scale of 75. After minimal stimuli attacks could develop where she appeared completely dazed. Neurological condition normal.

Case 138/56: 11-year-old girl with an I.Q. on the Grace Arthur scale of 71, who had "attacks where she appeared dazed". The teacher thought she had epilepsy. Neurological condition, including EEG, normal.

Case 47/57: Ten-year-old girl with an I.Q. on the Terman-Merrill scale of 64, who at times appeared "in a dream", far away, not hearing what was said, etc. Neurological condition, including EEG, normal.

Case 20/58: 17-year-old boy with an I.Q. according to Bellevue-Wechsler (C.V.B. method) of 78. On a number of occasions was in a dazed condition with irregular twitchings over the whole body. Neurological condition, including EEG, normal.

All these intellectually retarded patients except one have reacted with primitive attacks or states of bewilderment. This

is a way of reacting described as common in the state of mental insufficiency found in oligophrenics (Goldkuhl 1938).

Of the 22 intellectually normal children with physical symptoms, 9 were boys and 13 were girls. Among these also, similar primitive attacks and states of confusion were found in nine children (3 boys and 6 girls). These cases are discribed below.

Case 80/53: Seven-year-old girl. Since 1953 has had peculiar attacks at night. Screams, becomes stiff and rigid over the whole body and the eyes become fixed. Neurological condition normal.

Case 29/54: 13-year-old girl "screams, laughs and swears, running out into the garden" and appears confused. Neurological condition normal.

Case 21/55: 16-year-old girl. For the past two days has been in a complete state of confusion, talking incoherently, crying and withdrawn. Insomnia. Neurological condition normal.

Case 142/55: 14-year-old girl. "Particularly restless, walked up and down the whole day, thought everything appeared peculiar, felt herself to be in another world, thought that she would die or faint." Neurological condition normal.

Case 51/56: 15-year-old girl. Recently has had repeated "attacks" when she felt that "she would disappear", unable to feel her hands and feet, etc. In the past days appeared completely apathetic, lay in bed, reading was too much of an effort. Neurologically normal.

Case 141/56: Six-year-old boy. "According to the mother he is sometimes detached and gives wrong replies to questions." Neurological condition normal.

Case 50/57: Six-year-old boy "who on two occasions became extremely terrified". The parents rushed him to the medical out-patient department at the hospital. Physical and neurological condition normal.

Case 51/57: 16-year-old boy. "As he was falling asleep he became terrified, jumped up and was very agitated, said that he had murdered somebody and could not settle down again before the early hours of the morning. These states of agitation and confusion subsequently occurred every night." Neurological condition normal.

Case 31/57: 13-year-old girl. "Screams and kicks for hours at a time during the evenings and nights." Neurological condition normal.

Two cases with physical symptoms of psychogenic origin are described in greater detail. Both cases were girls with prolonged and debilitating illness.

Case 50/56: Ten-year-old girl, referred by the surgical out-patient department at the hospital because of an atypical disorder in walking, which began in connection with an injury to one knee. Nothing of interest known in the heredity. Parents healthy, father stated by the mother to be "very calm". Home normal. Pregnancy, delivery and early development quite normal. Previously physically normal. Always oversensitive but previously never had adaptation difficulties. Two months before admission injury to one knee, with moderate pain and possibly some swelling. Admitted to the surgical ward for 16 days, later treated as an out-patient with physical therapy, etc. Complained of severe pain locally the whole time, and limped. Objectively normal. In spite of this, delayed deterioration, so she was referred to the psychiatric department for investigation. — On admission there, pronounced limping sometimes of one leg and sometimes of the other. Walked swinging the whole body. Sometimes astasia-abasia.— During the stay in hospital, apart from the walking disorder, the physical condition was normal. Obviously sensitive, but no great adaptation difficulties, good contact with the staff and companions. She was observed to be an intellectually normal girl, reacting neurotically. This was considered to be caused mainly by her constitutional oversensitivity.—While in hospital she limped without change except when unaware of being observed, when she walked quite normally.—On discharge, about six weeks after

admission to the ward, the mother, for the first time conveyed that the father was a severe alcoholic, and he had been receiving treatment from an alcoholic clinic for several years. Since being informed that he had permanent liver damage he had begun drinking heavily again and had broken off contact with the clinic. According to the mother, when the father came home drunk, the patient had previously reacted by developing abdominal pain.—On discharge, the symptoms remained unchanged for about six months, but later gradually abated so that by the beginning of 1958 she was completely symptom-free. By this time the parents were divorced.

Case 70/56: 14-year-old girl, referred from the department of medicine at the hospital because of general tiredness. She was in hospital for a total of more than four months during 1956, for two periods with a two-months interval between them. Nothing of interest in the heredity, except that the mother had had a mild depression at puberty. During conversation she appeared depressed and stated that she was nervous and had difficulty in sleeping at night. The father was stated to be mentally normal and the home conditions were described as being good. Pregnancy and delivery normal. Walked early and mental development normal. Physically previously healthy. Appeared mentally normal, with no previous adaptation difficulties.—The present illness began in connection with a urinary tract infection during the autumn of 1955. After this she complained of tiredness, felt more and more lacking in enterprise, and by the end of October was forced to take to her bed. She constantly complained of pain, now here, now there. In the beginning of 1956 admitted and physically investigated at the Department of Medicine in the Hospital, where no organic basis for her symptoms could be shown. As a result of this she was referred to the Psychiatric Department for further investigation.—On admission complained and grumbled saying that she felt paralysed by tiredness. Was unable to be up and about, could not tolerate the slightest noise and refused all contact with staff and companions. After four days in the ward the parents took her home "since the hospital still seemed unable to help her". Not until two months later did the parents send word that they wanted her to be readmitted. During this time the patient was stated to have been constantly in bed, but on a number of occasions "possibly got up secretively" when the parents were out. On one occasion during 1956 her swimming costume was found wet on the airer.—When she was readmitted, her symptoms were, in the beginning, the same as before. She stubbornly refused to leave her bed except for short periods at a time. She was observed to be intellectually normal. There was no evidence that environmental disturbances were causing her condition. When the clinical diagnosis was discussed endogenous depression was thought most likely.—During the four months that she stayed in hospital the condition remained largely unchanged, even if her symptoms had become somewhat less severe. Thus, during the last few weeks, she was able to go to school accompanied by staff from the Department. As soon as she returned, however, she went back to bed. When she thought that she was not being watched she showed normal activity. On discharge there was no improvement in her condition. At that time she had been lying in bed during the greater part of the day for eleven months.—On discharge, contact was continued through the child-guidance clinic. A short time after, during one of the mother's visits to the clinic she informed the doctor that the father had been a severe alcoholic for many years and often came home drunk and disturbed the household. It was the mother's intention to apply for a divorce, and the father was no longer living at home. A short time later the patient began to improve relatively quickly, and at a check-up in the autumn of 1958 she was symptom-free.

In both these cases severe disturbance in the home was suspected at an early stage. In spite of intensive questioning and

despite a number of meetings with the mothers these suspicions could not be verified while the children were in hospital.

The other patients with physical symptoms had more simple but continuous symptoms. Umbilical-colic type of abdominal pain was found in five cases (2 boys and 3 girls), headache in four cases (3 boys and 1 girl) one of whom in addition, had giddiness and nausea (case 88/54). Finally, in two cases (1 boy and 1 girl) abdominal pain and headache occurred together.

In eight cases (5 boys and 3 girls), atypical symptoms were found. Pronounced aggressive symptoms occurred in three cases (2 boys and 1 girl) and hysterical symptoms in three cases (2 boys and 1 girl), of whom two showed a strong tendency to confabulate (cases 146/55 and 31/56). One four-year-old girl was severely retarded in her speech, but was otherwise normal in development. A two-year-old boy showed a picture of pseudo-imbecility during a stay in hospital of about two months, but at the end of this time his development, which had previously been greatly retarded, became normal.

Retarded Development

Sixteen patients (11 boys and 5 girls) had been referred, mainly because of clear developmental retardation. Even before admission it was easy to see that the majority of these patients were intellectually retarded.

Summary and Discussion

All the cases in the clinic material were referred by a doctor, 31 % by school doctors and 30 % by Children's Care Committee doctors. Of the subjects in Part I, only occasional cases had come in contact with school doctors, and of these, none had been referred to the child psychiatrist. In this series, the Children's Care Committee doctor had not referred any cases either. The reason for these differences between these series was probably that in the clinic series, about a half had shown anti-social characteristics, while in the randomly chosen series, only a few had done so.

It is seen that children with anti-social characteristics were admitted to a department of child psychiatry more easily than children with only symptoms of mental insufficiency.

Truancy and refusal to go to school were the commonest anti-social symptoms in the clinic series, and were found in 17 % of the school children. Twelve per cent of the children were guilty of pilfering or stealing and 9 % had run away. Sexual symptoms were described in 5 % of cases, while addiction (ethyl alcohol and "thinner") was found in two cases.

Out of the 80 cases who had mainly shown a picture of mental insufficiency, 29 had predominantly physical symptoms. This latter symptom-type was found significantly more often in girls than in boys, as opposed to general nervous symptoms, which appeared to the same extent in boys as in girls.

Among physical symptoms there were attacks of different kinds in 13 % of the total, abdominal pain, headache and giddiness, each in a few cases.

Two cases had had prolonged and hysterically-coloured conditions of insufficiency. Both were girls before puberty, living at home under conditions of great stress and becoming ill with physical

symptoms. Details of the father's alcoholism were only obtained at or after the patient's discharge from hospital. These two girls alone were in hospital for a total of 173 days. In spite of this, the essential cause of their symptoms, viz. the fathers' alcoholism, could not be found.

Clear inhibition of development was found more often in the clinic series than in the randomly-chosen subject material in Part I. Thirteen per cent of the clinic patients were referred mainly for this reason. The frequency of clear inhibition of development in the subject series in Part I was 2 %. The reason for this difference, of course, was that the majority of children, severely developmentally retarded, is investigated at a department of child psychiatry.

CHAPTER 7

PSYCHOLOGICAL INVESTIGATIONS

Psychometric Investigations

All of the 121 clinic patients except 12 were given intelligence or developmental tests of some kind. Those not tested were judged either to be of normal intelligence, or could not be tested for different reasons.

The most usual method of testing intelligence has been that of Terman-Merrill. Ninety four cases (66 boys and 28 girls) were tested in this way. Grace Arthur's performance test was used in seven boys. Two cases (1 boy and 1 girl), were tested according to Bellevue-Wechsler (C.V.B. method), three according to Bühler-Hetzer (boys) and one according to Gesell. One case was examined using Raven's matrices, and one according to Vineland social maturity scale.

The results of the intelligence tests according to the methods Terman-Merrill, Bellevue-Wechsler and Grace Arthur, expressed as I.Q. are set out in Fig. 2.

The figure shows that apart from cases of severe retardation of development, of which the majority were admitted for this reason, the distribution curve is normal.

Among the children examined according to Bühler-Hetzer, one 3.5-year-old boy received a D.Q. of 109 (Case 80/54), one three-year-old boy a D.Q. of 63 (Case 109/54) and one two-year-old boy a D.Q. of 84 (Case 71/55). The last case was a pseudo-imbecile boy who, during a four-month stay in hospital increased his D.Q. from 55 to 84. His later development was normal.

The nine-year-old boy, tested according to Raven, had normal intelligence (grade III +).

One boy, aged two years and eight months, tested according to Gesell, was given a developmental age of 18–24 months, and one boy aged three years and eight months, had an intellectual age of 1–1.5 years, according to the Vineland social maturity scale.

Special Psychological Investigations

The methods used here have been observation of sand-play ("The World"), together with the projective tests, Children's Apperception Test (C.A.T.), Thematic Apperception Test (T.A.T.), Picture Story Test according to Symond and Rorschach.

Observations of sand-play (at least three times) were made in 41 cases (30 boys and 11 girls) or about 34 % of the total.

C.A.T. was used 17 times (11 boys and 6 girls) or about 14 % of the total, T.A.T. in 14 cases (10 boys and 4 girls), i.e. about 12 % of the total. Symond Picture Story was used in examining four boys.

A Rorschach test was made on ten children (8 boys and 2 girls), i.e. on 8 % of the total.

It was sometimes considered sufficient,

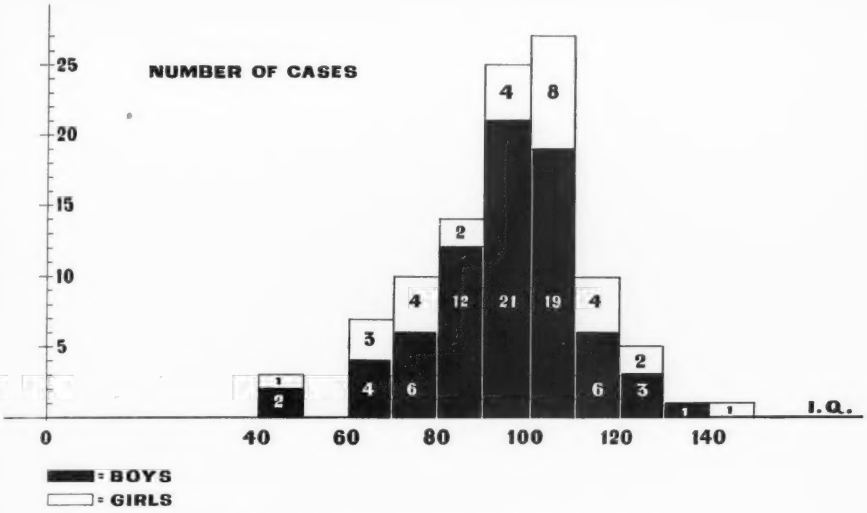

Fig. 2. Results of intelligence tests performed on the Clinic material.

especially in older children and adolescents, with conversation and observation in the ward. The procedure was the same with the cases of low intellect.

No attempt has been made to assemble and analyse the observations of sand-play. The material was both too small and heterogeneous for this. In addition, the recording of results was not standardised.

The records of C.A.T., T.A.T. and Picture-Story investigations, 35 cases in all, have been thoroughly examined without any single tendency being demonstrated.

In the T.A.T. records, it was stated that a number of the patients showed "blocking". In one case, "he can't get anything out" (Case 78/53), while in another "a very peculiar record. Out of ten pictures he can only talk about four" (Case 84/53) appeared.

The majority of the records are coloured throughout by a tone of depression and anxiety. There seldom appeared a disturbed emotional relationship with the father. In one case a strong relationship existed between the patient and the father (Case 36/54). The mother was mentioned in a number of records. In one, mention is made of "ambivalence or aggressiveness towards the mother" (Case 2/54) and another "presents the mother as unsympathetic" (Case 16/57).

The ten Rorschach records did not give any definite lead or unified picture either. It was noted of one 13-year-old boy that "the whole of his behaviour was normal" (Case 102/54). One 14 year old boy was described in the following way: "one can describe his case as being that of a normal puberty crisis" (Case 7/55). An 11-year-old boy was stated "not to be noticeably disturbed by the pictures, no long reaction times" (Case 81/55). A record of a 13-year-old girl reads "in conflict with the mother" (Case 129/55). A picture of anxiety with

depressive features occurs in one record of a 14-year-old girl without further guide to the aetiology being suggested (Case 142/55). Strong anxiety symptoms appeared in a 15-year-old boy where also "the mother is seen to be overbearing and overprotective" (Case 51/57).

Two records show signs of serious mental illness. One was of an eight-year-old boy whose record was described as seriously pathological (Case 34/58). In five pictures the patient saw "tattered objects and he also gives many anatomical answers". The other was an 11-year-old boy (Case 42/58) who was stated to be "suspicious, negativistic and out of touch with reality". In the nineteen cases in which the father's alcoholism was unknown while the patients were in hospital, only two were Rorschach tested (Cases 51/57 and 34/58). In one case the record was anxious in tone and the relationship with the mother was considered to be disturbed, while in another a diagnosis of psychosis was queried.

Summary and Discussion

One hundred and nine of the 121 clinic patients were psychometrically examined. Apart from those cases severely disturbed in their development, who were over-represented, the I.Q.s of the material were normally distributed.

The records from the psychological testing were reexamined. No single tendency was noticed. A disturbed relationship with the mother was found more often than with the father. No guide to the father's alcoholism or mental insufficiency was given by using these methods of psychological investigation.

CHAPTER 8

CLINICAL DIAGNOSES

A diagnosis was made in all except six cases (4 boys and 2 girls), who were only classified as "observation without fixed diagnosis" (cases 81/53, 155/55, 26/56, 51/56, 50/57 and 43/58). These cases consisted of a six-year-old boy with night terrors, a twelve-year-old boy with emotional outbursts, a three-year-old boy with motor restlessness, a fifteen-year-old girl with hysterical attacks, a six-year-old boy with acute attacks of anxiety and a nine-year-old boy with emotional outbursts. In all these cases the father's alcoholism was known at the hopsital, but investigations and observations were not considered to have given a basis for definitive psychiatric diagnosis.

A diagnosis of neurosis was made in 37 cases (21 boys and 16 girls), or 31 % of the total and the diagnosis "environmental damage", i.e. nervous symptoms without disturbance of the basic personality, in 32 cases (25 boys and 7 girls), i.e. 26 % of the total. In 16 cases (9 boys and 7 girls), or in 13 %, the diagnosis was neurosis with retardation of intellectual development and in 11 cases, or 9 % (9 boys and 2 girls), only retardation of intellectual development. Organic brain damage was diagnosed in eight of the patients (7 boys and 1 girl), and primary character disorder also in eight cases (6 boys and 2 girls). One boy had been diagnosed as having difficulty in reading and writing, another, schizophrenia (?), and a third, a girl who later was found to have a cerebral tumour, was diagnosed as acute encephalitis (?), cerebral tumour (??).

Of the 37 with neurosis, 14 (9 boys and 5 girls) were considered to be mainly caused by the home conditions (cases 74/53, 76/53, 78/53, 2/54, 9/54, 19/55, 25/55, 29/55, 49/55, 4/56, 50/56, 16/57, 132/57 and 49/58). Insufficient personality was considered to be the essential factor in seven cases (4 boys and 3 girls) (cases 71/53, 84/53, 114/54, 142/55, 169/57, 45/58 and 56/58). Puberty was considered to play a predominant role in two cases (1 boy and 1 girl) (cases 29/54 and 112/54). In the remaining cases of neurosis neither the home circumstances nor constitutional factors were of aetiological importance. Among the patients who were diagnosed as being injured by their environment, 16 (12 boys and 4 girls), or one half, were considered insufficient personalities (cases 36/54, 102/54, 7/55, 21/55, 81/55, 115/55, 134/55, 146/55, 12/56, 21/56, 31/56, 142/56, 25/57, 37/57, 41/57 and 42/58). One patient had had a cerebral contusion which was supposed to have been a handicap (case 114/54), but the home conditions were thought to be the cause of nervous symptoms in the remaining cases.

Of the cases with retardation of intellectual development who were given a

diagnosis of neurosis, one boy was also judged to have insufficient personality as well (Case 13/54). In three the neurosis were considered to be predominantly caused by the environment (cases 4/54, 11/55, and 103/55), but in the other cases there were other possible neurosis producing factors.

If one excludes the cases with retardation of intellectual development the diagnosis was made as follows:

Thirty two cases were diagnosed as insufficient personalities (23 boys and 9 girls) or 26 % of the total, of whom one quarter had primary personality disturbance.

In 30 cases, or about 25 % of the total (21 boys and 9 girls), the current home conditions were considered to be the cause of the nervous symptoms. Fourteen of these took the form of neurosis.

It is especially interesting to study the diagnosis in those 19 cases where the hospital was unaware of the father's alcoholism.

The diagnosis in five of these cases was retardation of intellectual development (cases 17/53, 30/53, 13/54, 42/54 and 130/55), and on admission, the question in every case was only that of where they should be placed.

The home circumstances were thought to be the cause of the patient's nervous difficulties, in six cases, in spite of the fact that the father's alcoholism was not known at the hospital (cases 80/54, 99/56, 115/56, 32/57, 51/57 and 66/58).

Definite brain damage occurred in three cases (cases 88/54, 88/56 and 141/56) with diagnoses of cerebral tumor (??) (diagnosis later verified), cerebral contusion and epilepsy (?).

Thus in these cases there was no doubt about the diagnosis. Indeed, in the majority of cases, knowledge of the father's alcoholism could not be said with any certainty to change the diagnosis or the attitude towards the case.

In one case a diagnosis of schizophrenia (?) was made.

Case 34/58: Nine-year-old boy without known hereditary mental illness. Father was an alcoholic for many years and known to the Temperance Board. Otherwise socially well adapted. Home conditions essentially normal but the patient left alone a great deal. Three elder siblings normal. Pregnancy and labour normal. Birth weight 3600 g. Breast fed for some months. At six weeks had gastro-enteritis, was admitted to hospital but was not generally seriously affected. Otherwise well. Began walking late, i.e. not until three years of age without support, but otherwise normal development. Always odd mentally. Precocious in some respects, childish in others. No contact with companions of the same age. Motor restlessness, sometimes had had anxiety attacks. Referred with the query: Is he ready for school? At the clinic obsessional and compulsive, at times bizarre with neologisms and peculiar staccato speech. Sometimes inexplicable panic reactions, especially when he saw broken objects. Emotions often completely inadequate. At times completely withdrawn. I.Q. on the Terman-Merrill scale 101, but nevertheless not considered ready for school. Summarised in the case notes: "Pronounced and bizarre symptoms shown by the patient, cannot be accepted as simply neurotic, particularly as no likely aetiological factors in the environment can be found."

Even if the father had been known to be an alcoholic, a diagnosis of schizophrenia (?) was considered to be justified.

Primary character disorder were diagnosed in three cases.

Case 157/57: 14-year-old boy. Nothing of interest in the heredity. Parents and home circumstances described as normal but the father was registered at the Temperance Board as an alcoholic. Since the age of 3–4 different kinds of difficulties in adaptation, with companions and in school. In the last year has also begun to pilfer. Complained of headache and stomach-ache and began to stutter. For the last four years has been under treatment at the child-guidance clinic, without anyone there knowing of the father's alcoholism. Thought to have a primary personality disturbance, both by the child-guidance clinic and by the hospital. Intellectually normal.

Case 14/58: 13-year-old boy. Nothing of interest in the heredity. Parents divorced but the patient still has regular contact with the father. The latter is registered at the Temperance Board as an alcoholic. Because of the mother's employment away from the home, the patient was often left to wander about. Mentally always uneasy, impulsive, difficult to bring up. Difficulty with companions, and could not keep up in the school in spite of normal intellect. On examination at hospital, emotionally unstable, poor self-control and general immaturity. Thought to have a primary personality disturbance with a possibility of neurosis also.

Case 26/58: 16-year-old girl. Nothing of interest in the heredity. Parents and home conditions stated to be normal. Father was known to the Temperance Board as an alcoholic. Patient had always been hysterical, more so in recent years. In addition pilfered and showed sexual instability. Often hysterical attacks. Normal intellect, but hysteroid. Diagnosis of primary personality disturbance.

In hardly any of these cases had knowledge of the father's alcoholism changed either the attitude or the diagnosis. The first and the last cases cannot have any other diagnosis but that of primary character disorder. In the other case even without knowledge of the father's alcoholism the home circumstances had been so disturbing as to have been of importance in discussion of the diagnosis.

A diagnosis of neurosis had been made in only one case. This was considered mainly to have been caused by puberty.

Case 112/54: 15-year-old boy. Nothing of interest in the heredity. Parents and home conditions stated as normal, but the father was registered at the Temperance Board as an alcoholic. During recent years a number of difficulties in social adaptation. Diagnosis was: "Puberty neurosis". Intellectually normal.

Thus only in the last case could the diagnosis have been different if one had known of the father's alcoholism.

Measures Taken or Suggested

Continued contact with the child-guidance clinic was recommended for 34 children (19 boys and 15 girls) or in 28 % of the total.

A change of class or school was suggested in 22 cases (17 boys and 5 girls) or in 18 % of the total.

Placing in a foster home was recommended in 28 cases (18 boys and 10 girls) or in 23 % of the total, and in institutions in 32 cases (25 boys and 7 girls) or in 26 % of the total.

It is thus seen that 60 children, or about half of the total were recommended to be sent away from home. The suggested institutionalisation is set out in Table 38. Of these suggestions, about half of them could be carried out after bringing pressure to bear to take the child into protective custody.

In the case of five children (4 boys and 1 girl) the parents broke off contact with the hospital before the investigation was

TABLE 38. *Type of institutional care advised for patients on discharge from the Clinic.*

Institution advised	Boys	Girls	Total
Childrens' home	5	2	7
Detention home[1]	3	1	4
Treatment home (for socially maladapted children)	3	0	3
School for imbeciles	3	3	6
Home for care of imbeciles	4	1	5
Home for nervous and psychopathic children	3	0	3
Home for easily managed insane children	3	0	3
Institution for epileptics	1	0	1
Total	25	7	32

[1] Ungdomsvårdsskola.

completed, but compulsive measures were not considered justifiable.

Summary

On discharge from hospital, a diagnosis had been made in 95 % of cases. The commonest diagnosis was neurosis, in 44 % of the total. However, a third of these consisted of patients with retardation of intellectual development.

Environmental injury was the reason given in 26 % and primary character disorder in 7 % of cases. A diagnosis of brain damage had been made in 7 % of the total.

Retardation of intellectual development alone, occurred in 9 % of the series.

Apart from the patients with retardation of intellectual development, 26 % of the total were judged as having insufficient personalities. As mentioned above, a quarter of these had primary disturbance of personality.

Only in 25 % of cases was the home environment considered to have a crucial importance for the development of nervous symptoms.

In those 19 cases, where the father's alcoholism was unknown to the hospital, the diagnosis would hardly have been different even had the father's alcoholism been known, because other severe environmental disturbances occurred at the same time, and these were noticed.

On discharge, continued contact with the child-guidance clinic was recommended in 28 % of the total. Change of class or school was suggested in 18 %. Transfer of the child was prescribed in about a half of the total. Of the latter, about a half were placed with help of compulsive measures, in the form of being taken into protective custody.

CONCLUSIONS

A large number of the children admitted to the Department of Psychiatry at K.L. B. consisted of children of chronic alcoholics. The frequency of divorce in the families of these children was remarkably high. The commonest cause of the child's being admitted for investigation was antisocial symptoms of different kinds, such as adaptation difficulties in school, truancy, pilfering, stealing, running away, sexual instability, etc. The preceding part of the investigation showed that mental insufficiency was more common among boys from broken homes than among boys from unbroken homes. On the other hand, no corresponding difference between the groups of girls was found. In addition, it was shown that adaptation difficulties were more common among boys than among girls. It would therefore be expected that there were more boys than girls in the clinic material. Such was, indeed, the case.

In many cases, the symptom picture presented by these children is difficult to interpret, because it is dominated by physical symptoms. The latter, which appear more commonly among girls than among boys, often cause extensive, time-consuming and unnecessary investigations.

The clinical investigation seldom leads one to the father's alcoholism. Since the children's parents, besides, co-operate badly throughout, in many cases, the fathers' alcoholism has remained obscure during the whole time that the children have been in hospital. In this way, the clinical investigation has been incomplete and the treatment of the child inadequate.

One of the causes of the defective co-operation of the parents, has probably been that the alcoholic father lacked insight into the illness or felt himself incapable of giving up his alcoholic habits. In addition, the wife clearly backed him up, often because of fear of reprisals if she should give him away. In favour of the latter was the fact that children who were admitted to hospital of their own free will, because of general symptoms of nervousness, almost always came from divorced homes, where the mother looked after the child alone.

Because of the above, during child-psychiatric investigation in Sweden, a check must always be made in the Temperance Board's register, to see whether the child's parents are registered there as alcoholics. However, not all alcoholic parents will come to light, even by this means. In both the subject series in Part I and in the clinic material, about a third of the alcoholic fathers were not registered with the Temperance Board. In such cases, the mental symptom-picture in the children can be of great help in revealing very bad home conditions, including alcoholism. Intensive, prolonged and treatment-resistant symptoms, such as headache, abdominal pain, general tiredness, attacks of different kinds, disorders in walking, etc., should always arouse sus-

picions of severe disturbances in the home, if the physical examination has given no explanation of their cause.

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APPENDIX

Questionnaire

Case no. . . . . ((N.B. siblings same no. a, b, c) Exam. date . . . . .

Particulars

Name: . . . . . .

Born: . . . . . Age: . . . . . .

Father: . . . . . Born: . . . . married unmarried divorced dead

Mother: . . . . . Born: . . . . married unmarried divorced dead

Father's (mother's) work: . . . . . .

Address: . . . . . Tel. no. . . . .

School: . . . . . Class: . . . .

Teacher: . . . . . Tel. no. . . . .

Height: . . . . . Weight: . . . . . .

Code:

Paternal grandparents and maternal grandparents

Epilepsy: . . . . . .
Encephalitis: . . . . . .
Other organic nervous disease: . . . . . .
Asthma: . . . . . .
Eczema (not neonatal): . . . . . .
Diabetes mellitus: . . . . . .
Peptic ulcer: . . . . . .
Headache: . . . . . .
Abdominal pain: . . . . . .
Tiredness: . . . . . .
Heart pain: . . . . . .
Enuresis: . . . . . .
Encopresis: . . . . . .
Anxiety symptoms: . . . . . .
Depressive symptoms: . . . . . .
Hysterical symptoms: . . . . . .
Obsession-Compulsion symptoms: . . . . . .
Psychotic symptoms: . . . . . .
Asociability: . . . . . .
Alcoholism: . . . . . .
. . . . . .
Speech disorder: . . . . . .
Left-handedness: . . . . . .
Sleep disorder: . . . . . .
Reading and writing difficulties: . . . . . .
Oligophrenia: . . . . . .

Father's alcoholism and its duration

. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .

Home conditions

Born legitimate — illegitimate. The child is no. . . . / . . . siblings.
The parents live together — divorced — since . . . . . .
The mother is employed full-time — half-time — not at all (the last year)
Home : . . . . . rooms and kitchen. Number of family: . . . . . .
Siblings:

	Sex	Age	Status of physical and mental health
No. 1.:			
No. 2.:			
No. 3.:			
No. 4.:			
No. 5.:			

Stay away frome home (more than 3 months)
1 . . . . . .
2 . . . . . .
3 . . . . . .
Stay at day-nursery (more than 6 months) . . . . . .
Stay at afternoon-nursery (more than 6 months) . . . . . .

Child's early development

Mother pregnant — not pregnant — at marriage
Pregnancy (infections, mental symptoms): . . . . . .
. . . . . .
Delivery: . . . . . .
Birth weight: . . . . . .
Condition at birth: . . . . . .
Neonatal period: . . . . . .
Feading: . . . . . .
Weaning: . . . . . .
Sleep during first year of life: . . . . . .
Walked without support at . . . . . months.
Spoke sentences at . . . . . months.
Dry at . . . . . .
Clean at . . . . . .

Child's state of physical health

Admitted to hospital or to doctor (when, where, why): . . . . . .

Ordinary children's illnesses (when): . . . . . .

Upper respiratory tract infections (once/month or more often during the winter half of the year): . . . . . .

Epilepsy, convulsions: . . . . . .

Head injuries (unconscious): . . . . . .

Tics: . . . . . .

Addiction (tablets, thinner etc.): . . . . . .

Headache: . . . . . .

Abdominal pain: . . . . . .

Joint pains, "growing pains": . . . . . .

Muscle pains (grinds teeth): . . . . . .

Palpitations, feelings of suffocation or oppression: . . . . . .

Nausea, vomiting: . . . . . .

Diarrhoea/constipation: . . . . . .

Tiredness: . . . . . .

Hypo/hyperthyroidism: . . . . . .

Growth disorder: . . . . . .

Other remarks: . . . . . .

Child's state of mental health

(state whether the symptoms are present now)

Examined or admitted for nervous disorders: . . . . . .

. . . . . .

Finger sucking: . . . . . .

Nail biting: . . . . . .

Enuresis: . . . . . .

Encopresis: . . . . . .

Night terrors: . . . . . .

Somnambulism: . . . . . .

Other sleep disorders: . . . . . .

Stuttering: . . . . . .

Masturbation: . . . . . .

Lefthandedness: . . . . . .

Confabulation: . . . . . .

Emotional instability: . . . . . .

Difficulties in concentrating: . . . . . .

Motor restlessness: . . . . . .

Anxiety symptoms: . . . . . .

Obsession compulsion symptoms: . . . . . .

Depressive symptoms: . . . . . .

Hysterical symptoms (hysterical outbursts, attacks, simulation, exaggravation of symptoms): . . . . . .

Aggressiveness: . . . . . .

Difficulties in upbringing: . . . . . .

Difficulties in getting on with siblings: . . . . . .

Difficulties in getting on with companions: . . . . . .

Adaptability in the nursery, kindergarten, etc.: . . . . . .

. . . . . .

Way of reacting to stress: . . . . . .

Refusal to eat: . . . . . .

Overeats: . . . . . .

School conditions

Began school at . . . . . years of age.
Kept down: . . . . . .
Special class: . . . . . .
Hates school: . . . . . .
Difficulties with companions: . . . . . .
. . . . . .
Judgement of the techer: deviates — does not deviate from companions.
If so, in which way: . . . . . .
. . . . . .

Social adaptation

(see above under "home conditions", "state of mental health" and "school conditions")
Truanted: . . . . . .
Pilfered: . . . . . .
Ran away: . . . . . .
Burgled: . . . . . .
Committed arson: . . . . . .
Abusus, addiction: . . . . . .
C.C.C. notified because of misbehaviour: . . . . . .
. . . . . .
Police notified because of antisocial behaviour: . . . . . .
. . . . . .

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PAPERS PRESENTED AT THE
IX INTERNATIONAL CONGRESS OF PAEDIATRICS
AT MONTREAL, JULY 1959

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Problems and Progress of Neonatal Paediatrics

Symposium, July 21, 1959 at the IX International Congress of Paediatrics at Montreal

CHAIRMAN: Clement A. Smith, Boston

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From the Department of Biological Chemistry, Harvard Medical School and the Research Laboratories of the Boston Lying-in Hospital, Boston, Massachusetts

The role of anaerobic metabolism in fetal and neonatal survival*

by CLAUDE A. VILLEE

Just a century ago Pasteur showed that the production of ethanol from glucose by yeast can occur under anaerobic conditions and emphasized the importance of the finding that living tissue can draw nourishment and energy from glucose in the absence of oxygen. Pasteur recognized that other living cells which ordinarily require oxygen for normal function and growth can also derive energy from glucose by metabolizing it under anaerobic conditions. Experiments in the past century have shown that both unicellular and multicellular organisms can metabolize glucose and other sugars anaerobically. Meyerhof (1930) was one of the first to demonstrate that extracts of mammalian muscle can convert glycogen to lactic acid under anaerobic conditions. Liver, kidney, brain, and other mammalian tissues share this property.

It is now quite clear that the first dozen or so enzymatic steps in the metabolism of glucose to pyruvate and lactate are identical in the presence or absence of oxygen. The resemblance does not end there, for pyruvate can be metabolized under anaerobic conditions, at least to some extent, to substances other than lactate.

A tissue deprived of oxygen does not immediately cease metabolizing. Most of the reactions of intermediary metabolism do not require molecular oxygen as a reactant and they will continue in its absence. The term *anaerobic metabolism*, referring to those reactions which proceed in the absence of molecular oxygen, is very broad and non-specific. Any organism or tissue existing under anaerobic conditions must convert some of the potential energy of its substrate molecules into biologically useful energy without having to use molecular oxygen. In other words, hydrogens and electrons must be removed from substrate molecules and transferred to some acceptor other than to oxygen to produce water.

The ability of the newborn mammal to withstand severe hypoxia is well established. Newborn rats and mice, or fetuses obtained by Cesarean section shortly before birth, will survive 45 minutes in an atmosphere of pure nitrogen, 5 hours in 2 per cent oxygen and 15 hours in 5 per cent oxygen (Himwich, Alexander, and Fazekas, 1941; Kimmelstiel and Villee, 1956; Roux and Villee, 1959). This ability to survive prolonged oxygen deprivation declines rapidly after birth and disap-

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pears after the first few weeks of life. It might conceivably be due to some unique reaction not present in adult tissues but there is no evidence which suggests that this is true. Or the fetus might differ quantitatively from the adult in certain enzymatic processes present in all tissues. As a third alternative, the fetus might have a lower rate of metabolism, or it might be able to decrease its rate of metabolism without harm and in this way be better able than the adult to withstand the deprivation of oxygen (Fazekas, Alexander, and Himwich, 1941; Cross, Dawes, and Mott, 1959).

The classic experiments of Himwich and his colleagues (1941) had shown that the ability to resist hypoxia is not decreased by the injection of cyanide, which inhibits cytochrome oxidase, but it is greatly reduced by the injection of iodoacetic acid or fluoride, which inhibit enzymes in the glycolytic cycle. Himwich concluded that the resistance to hypoxia is independent of the cytochrome system but depends in part on the energy derived from an accelerated rate of glycolysis.

There have been several suggestions that the tissues of the fetus and newborn have some special pathway of anaerobic metabolism. It was suggested (Räihä, 1954), for example, that the fetus might obtain oxygen by converting carbohydrate to fat:

$$17\ C_6H_{12}O_6 \rightarrow 2\ C_{51}H_{98}O_6 + 4\ H_2O + 43\ O_2$$

There is, however, no reaction known in mammalian tissues in which molecular oxygen is evolved. The conversion of glucose to fat does not produce oxygen, but produces carbon dioxide and water as byproducts:

$$25\ C_6H_{12}O_6 + 5\ O_2 \rightarrow 2\ C_{51}H_{98}O_6 + 48\ CO_2 + 52\ H_2O$$

Hydrogen atoms given off in the reactions of glycolysis or elsewhere might be utilized in the synthesis of fats, for hydrogen is required for the synthesis of fatty acids from the two-carbon unit acetyl co-enzyme A. In a sense, the synthesis of fat provides a hydrogen "sink", a depot for hydrogen atoms, which is an alternative to their combination with oxygen to form water. Recent advances in our knowledge of the details of fatty acid synthesis have shown that the reactions require energy in the form of ATP. Thus, although lipogenesis might utilize the hydrogens released in glycolysis and prevent the accumulation of toxic amounts of lactic acid, the process would not provide for a net release of energy under anaerobic conditions.

The reactions of the glycolytic cycle (Figure 1) may occur either in the presence or the absence of oxygen. The enzymes involved and the intermediate substances formed are exactly the same under aerobic or anaerobic conditions. Molecular oxygen, you will note, is not involved in any of these reactions. Thus, the differentiation commonly made between "aerobic" and "anaerobic" glycolysis is misleading. Glycolysis is commonly measured by the rate of accumulation of lactic acid. Lactic acid, however, may be produced from pyruvic acid derived from alanine or from oxaloacetic acid as well as from that produced from hexoses, so that we cannot accept the rate of accumulation of lactic acid as an exact measure of the rate at which hexoses have been metabolized in the glycolytic cycle.

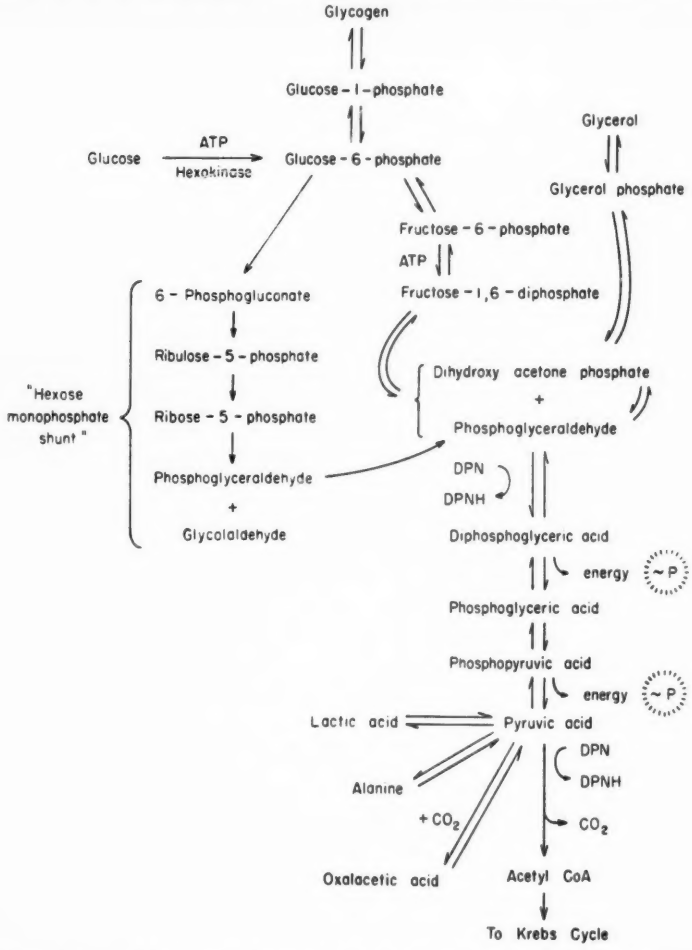

Fig. 1. Diagram of some of the intermediates in the glycolytic cycle and in the hexose monophosphate shunt.

The amount of oxygen available does, in large measure, determine the amount of lactic acid that accumulates. Lactic acid is derived from pyruvic acid by the addition of two hydrogens from reduced diphosphopyridine nucleotide (DPNH) by the enzyme lactic dehydrogenase. When adequate amounts of oxygen are present, the reduced DPN is oxidized by other enzymes, and therefore, is not available to convert pyruvate to lactate. Because of this, measuring the lactic acid content of a tissue does give a rough estimate of how much oxygen was available to it in the preceding period.

Energy is released as ATP at two points

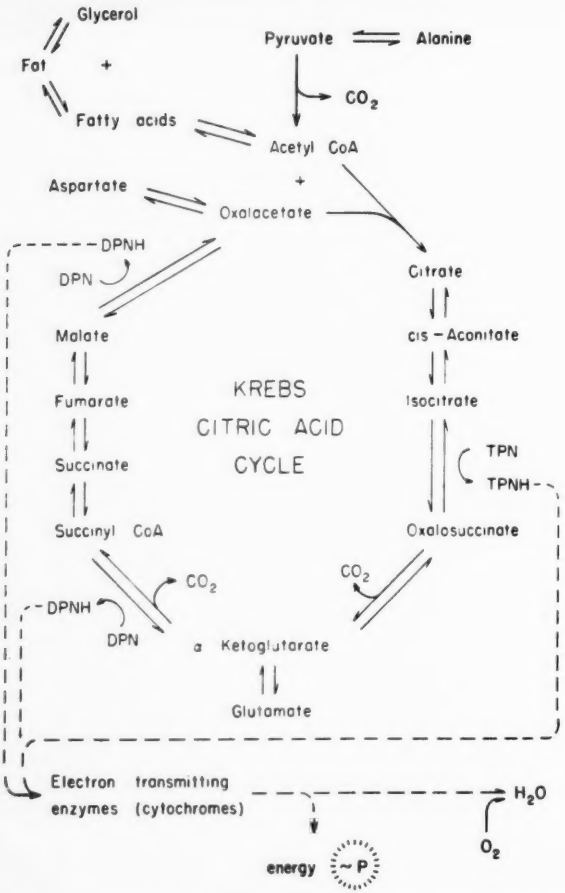

Fig. 2. Diagram of the intermediates in the Krebs citric acid cycle.

in the glycolytic cycle (Figure 1). Two energy-rich bonds are released per triose metabolized, or four per hexose. But two ATPs are required to get glucose into the glycolytic cycle, one to convert glucose to glucose-6-phosphate and one to convert fructose-6-phosphate to fructose-1, 6-diphosphate. Hence, the net yield to the tissue from converting one mole of glucose to two moles of pyruvate is two energy-rich phosphates. Energy for the synthesis of molecules, for the transmission of a nerve impulse, the contraction of a muscle, or any other process, must be present in these handy little bundles called energy-rich phosphate bonds.

Figure 2 illustrates some of the steps by which pyruvate is metabolized first to acetyl coenzyme A, and subsequently, via the citric acid cycle, to carbon dioxide.

TABLE 1. *Analyses of new-born rats kept in oxygen or nitrogen atmosphere.*

	In oxygen	In nitrogen
Liver Glycogen, mg. per gm. liver	30.2	18.4
CO_2 Given off, mM. per Kg. rat	14.4	4.1
Blood Glucose, mg. per 100 ml.	81	86
Blood Lactate, mg. per 100 ml.	27	123
Carcass Fats mg./gm.	15.9	8.2
c/m/gm. fat*	510	450
Liver Fats mg./gm.	35.2	30.0
c/m/gm. fat*	1500	1550

* Counts per minute and gram fat.

In the course of these reactions, additional hydrogen atoms are removed and transferred to a hydrogen acceptor such as a pyridine nucleotide. As long as there is a supply of oxidized pyridine nucleotide, DPN or TPN, this cycle will continue even in the absence of molecular oxygen. Cells in general have only a limited amount of pyridine nucleotides and these must in turn pass the hydrogens on to another acceptor. Under aerobic conditions the ultimate hydrogen acceptor is oxygen. Oxygen is not involved as a reactant in any of the steps of the citric acid cycle. The hydrogens released from the substrate and transferred by way of TPN or DPN and the electron transmitting system eventually react with molecular oxygen to form water. A large amount of biologically useful energy is released as ATP as electrons flow through the electron transmitting system from the pyridine nucleotides to oxygen; some three energy-rich phosphate bonds are produced for each pair of electrons—a total of 15 energy-rich bonds for each pyruvate completing one turn of the citric acid cycle or 30 for the two pyruvates formed from a molecule of glucose. Six additional energy-rich bonds are formed as the hydrogens given off in glycolysis are passed through the electron transmitter system. The sum, 36 + 2 or 38, is made available to the cell when glucose is oxidized completely. The electron transmitter system is not more efficient than glycolysis in the production of energy-rich phosphates; the thermodynamic efficiency of the two systems is comparable.

In our initial experiments (Kimmelstiel and Villee, 1956) newborn or fetal rats were injected with labeled pyruvate and placed in a respiratory train in an atmosphere of oxygen or nitrogen for 30 to 45 minutes, then sacrificed. The results are summarized in Table 1. Animals kept in nitrogen had much less glycogen in the liver and exhaled much less carbon dioxide. The carbon dioxide given off is formed by the decarboxylation of pyruvic and other organic acids and these decarboxylation processes continue in the absence of oxygen as long as there is some oxidized pyridine nucleotide to accept the hydrogens formed in the coupled reactions. The glucose content of the blood was not affected by hypoxia, which suggests that the limiting factor in survival under these conditions is probably not the supply of glucose in the blood. If the

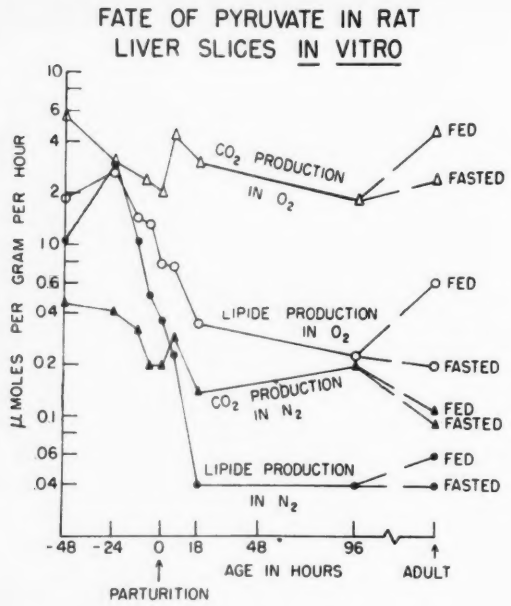

Fig. 3. Conversion of pyruvate-2-C^{14} to carbon dioxide and lipid by liver slices from fetal, newborn, and adult rats, incubated in oxygen and nitrogen.

greatly increased concentration of lactic acid in the blood of the hypoxic animals is taken as representing the concentration in the total extra- and intracellular fluids of the body, then the total lactic acid produced just about accounts for the glycogen that disappeared from the liver during hypoxia. The conversion of this amount of glycogen to lactic acid would release about 0.5 calorie per 5 gm. rat during the 30 minutes of anoxia. It is unlikely that this amount of energy would suffice for the observed survival of the ratlet during the 30 minute period.

Direct determinations of the energy relationships involved would help settle the question of whether survival results from a decreased rate of metabolism or from an altered pattern of metabolism which maintains the same caloric output.

Dr. Dwain Hagerman in our laboratory is now attempting to measure directly the amount of heat given off by newborn and fetal rats under aerobic and anaerobic conditions. There are many technical difficulties involved in these measurements because of the small amount of heat

TABLE 2. *Conversion of glucose to pyruvate by liver slices.*

	In O_2	In N_2
Fetal liver	0.53 ± 0.07	3.07 ± 0.3
Newborn liver	0.44 ± 0.06	1.72 ± 0.2
Adult liver	0.41 ± 0.06	1.04 ± 0.1

Values are expressed as μmole/gm. tissue/hr.

transferred and so far the attempts have not been successful.

In another series of experiments, liver slices from fetal, newborn, and adult rats were incubated in carbon-14 labeled pyruvate (Villee and Hagerman, 1958). The rate of lipid production was roughly ten-fold greater in the fetus just before birth than it was in the adult (Figure 3). In the fetal liver just before birth, the rates of lipid synthesis in oxygen and in nitrogen are of about the same order of magnitude. The rate of lipogenesis decreases at birth and by 18 hours after birth lipogenesis occurs anaerobically at only one-tenth the aerobic rate. This is a biochemical process which decreases very rapidly after birth, as does the resistance to hypoxia. It would be very tempting to postulate that this process has something to do with the resistance to hypoxia. However, to explain the resistance to hypoxia the fetus should have some process that proceeds more rapidly under anaerobic conditions than under aerobic conditions, not merely one that occurs at the same rate. Furthermore, this increased rate of metabolism, whatever its nature, would have to be some process which would lead to the release of biologically useful energy.

To measure the glycolytic rate as directly as possible, slices of fetal, newborn or adult rat livers were incubated in flasks containing uniformly labeled C^{14} glucose. At the end of the hour's incubation, pyruvate was isolated from the incubation medium as the dinitrophenylhydrazone. The amount of glucose converted to pyruvate per hour and gram of tissue is shown in Table 2. Glucose was metabolized to pyruvate at comparable rates in fetal and adult livers under aerobic conditions. However, the ratio of anaerobic to aerobic glycolysis was nearly 6 in the livers of 3 to 4 gram fetuses, 4 in the livers of newborn rats, and only 2.5 in the livers of adult rats. It seems clear that the glycolytic enzymes of the fetal liver respond to anaerobiosis more effectively than do those of the adult liver.

There is a widely quoted statement that fetal tissues are less active than the comparable adult tissue. Fetal brain does indeed have a lower metabolic rate than adult brain, but the activities of fetal and adult human liver, summarized in Table 3, are quite comparable. Their oxygen consumptions are very similar. Adult liver has a higher glycogen content and a higher rate of glycogen utilization. The higher rate of glucose production in adult liver is a reflection of the greater activity of the enzyme glucose-6-phosphatase in the adult than in the fetal liver. The rate of production of lactic acid is about the same in fetal and adult livers incubated in oxygen but is much greater in fetal than in adult liver when they are incubated in nitrogen. Human fetal tissues, like those of the rat, are characterized by an increase in lactic acid production in response to anaerobiosis which is markedly greater than that of adult tissues.

Measurements have been made in several different laboratories of cerebral blood flow and of arterio-venous differences in oxygen and glucose content (Kety and Schmidt, 1948; Gibbs, Lennox, Nims and Gibbs, 1942, cf. Lassen, 1959). From these it has been calculated that the normal adult human brain consumes, on the average, 3.5 ml. of oxygen and 5.5 mg. of glucose per minute per 100 gm. of tissue.

TABLE 3. *Metabolism of human liver slices in vitro.*

	Fetal liver oxygen	Incubated in nitrogen	Adult liver oxygen	Incubated in nitrogen
Substrate: Glucose C^{14}, uniformly labeled				
R.Q.	1.31	—	0.95	—
Oxygen consumption	28.4	—	28.4	—
Glycogen utilization	−54	−68	−114	−155
Glucose production	+13	+14	+50	+73
Glucose utilization	0	−12	−15	−17
Lactate production	+17	+52	+21	+38
Conversion of carbon of glucose to lipid	0.23	0.03	0.15	0.11
Conversion of carbon of glucose to carbon dioxide	0.41	0.08	0.20	0.10
Substrate: Acetate-2-C^{14}				
R.Q.	1.19	—	0.96	—
Oxygen consumption	28.4	—	30.1	—
Glycogen utilization	−40	−52	−114	−116
Lactate production	+16	+40	+18	+34
Conversion of carbon of acetate to lipid	1.42	0.08	0.042	0.0065
Conversion of carbon of acetate to carbon dioxide	0.66	0.065	0.245	0.074

Initial content of glycogen: Fetal liver, 100 μmoles/gm wet tissue.
Adult liver, 200 μmoles/gm wet tissue.
All values except R.Q. are expressed as μmole/gm tissue/hr.

This can be converted to 156 micromoles of oxygen and 30 micromoles of glucose per minute and 100 gm. of tissue. The rate of oxygen utilization is slightly less than the theoretical amount (180 micromoles) required for the complete conversion of glucose to CO_2. The remaining glucose is probably metabolized to pyruvate and lactate and leaves the brain in this form.

Fetal cerebral cortex slices incubated *in vitro* utilize on the average 25 micromoles of glucose per 100 gm. and minute, a value very similar to the 30 micromoles found for adult brain *in vivo*. This suggests that hexokinase and the enzymes of the glycolytic cycle of the fetal brain are operating at rates comparable to those in adult brain. However, the oxygen consumption of the fetal brain slices was only

TABLE 4. *Metabolism of fetal liver (age 20 weeks) in oxygen after incubation in oxygen or nitrogen.*

First hour Incubated in	Second hour	Oxygen used	Glycogen used	Pyruvate used	Lactate made	Carbon of acetate converted to carbon dioxide	Carbon of acetate converted to lipid
Substrate: Acetate-2-C^{14} + Pyruvate							
Oxygen	—	35	26.5	29	22	0.47	1.07
Nitrogen	—	—	49	19	43	0.09	0.07
Oxygen	Oxygen	29	48	27	17	0.51	0.79
Nitrogen	Oxygen	24	62	17	16	0.31	0.84

All values are expressed as μmole/gm tissue/hr.

TABLE 5. *Metabolism of fetal cerebral cortex (age 25 weeks) in oxygen after incubation in oxygen or nitrogen.*

First hour Incubated in	Second hour	Oxygen used	Pyruvate used	Lactate made	Carbon of acetate converted to carbon dioxide	Carbon of acetate converted to lipid
		Substrate: Acetate-2-C^{14} + Pyruvate				
Oxygen	—	16.2	17.6	4.0	0.19	0.005
Nitrogen	—	—	10.9	5.5	0.04	0.0015
Oxygen	Oxygen	9.6	11.8	1.7	0.11	0.0017
Nitrogen	Oxygen	7.8	7.9	2.0	0.08	0.0017

All values are expressed as μmole/gm tissue/hr.

37 micromoles per 100 gm. and minute, whereas complete oxidation of the glucose taken up by the slices would require oxygen consumption at a rate of 150 micromoles per 100 gm. and minute. The remainder of the glucose is converted to lactate by the cerebral cortex and the rate of lactate production, 42 micromoles per 100 gm. and minute, accounts for the remainder of the glucose.

Thus, although the enzymes for the uptake of glucose appear to be operating in the fetal brain at rates remarkably similar to those in the adult, the rate for the utilization of oxygen is much smaller. It appears that some step in the oxidative pathway is rate-limiting for the utilization of oxygen, even when the tissue is incubated in an atmosphere of pure oxygen.

There is a widespread belief that anoxia, even of short duration, irreparably damages tissues. To test this, slices of fetal liver or brain (from fetuses of 20 to 25 weeks gestation) were placed in Warburg vessels and half of the vessels were gassed with oxygen and the other half with nitrogen. After an hour's incubation, slices from two oxygen vessels and from two nitrogen vessels were removed, placed in fresh incubation medium in other vessels, gassed with oxygen and incubated for a second hour. The experiment thus provides a comparison between the metabolism during the second hour of tissues that had spent the previous hour in either oxygen or nitrogen.

Table 4 shows that the oxygen consumption of liver slices that had been anaerobic the previous hour was about 80 per cent as great as that of the tissues in oxygen the previous hour. The slices that had been in nitrogen utilized less pyruvate but made as much lactate a those previously in oxygen. The rate of metabolism of acetate to carbon dioxide, a measure of the activity of the enzymes of the citric acid cycle, shows that the slices that had been anaerobic were not quite as active as the ones that had been aerobic the previous hour. However, their ability to convert labeled acetate to fatty acids was equal to or even greater than the ability of the slices kept in oxygen. Thus, the liver slice that had spent a full hour in complete anoxia had many of its enzymatic functions intact.

Since brain cells are believed to be exceptionally sensitive to oxygen deprivation, comparable experiments, summarized in Table 5, were performed with slices

of fetal cerebral cortex. Slices kept in nitrogen subsequently utilized oxygen at about 80 per cent of the rate of those kept in oxygen; they utilized less pyruvic acid and converted somewhat less acetate to carbon dioxide but produced about the same amount of lactic acid and converted similar amounts of acetate to lipids. Thus, like the liver, the cells of the cerebral cortex of the fetus are still quite active after an hour of complete anoxia. We have, of course, no evidence that these brain cells could still initiate or transmit nerve impulses.

Histologic comparison of the condition of tissues after aerobic and anaerobic incubation revealed very little difference between the two and very little difference from unincubated tissue. The cells of the tissues incubated in nitrogen show some blank spaces which are interpreted as regions from which glycogen has been removed. Chemical analysis reveals that there was much less glycogen in the anaerobic slice than in the aerobic one.

These experiments have been repeated a number of times with consistent results. They have been extended to include other tissues and other substrates. In each case the tissue after an hour's anaerobiosis was essentially as active in these basic metabolic reactions as was the control slice after an hour's incubation in oxygen. In some experiments, tissues were incubated in oxygen or nitrogen for two hours, aliquots were taken for chemical analyses and the vessels were then gassed with oxygen and incubated for a third hour. The oxygen consumption during the third hour of both the tissues that had been aerobic and those which had been anaerobic the previous two hours was similar but at a rate only 55 per cent as great as that of the aerobic tissue during the first hour of incubation. Although the tissue after two hours of nitrogen respired as well as the control tissue after two hours of oxygen, it converted pyruvate to carbon dioxide at one third the rate and pyruvate to lipid at 10 per cent of the rate of the control tissue. Thus two hours of anoxia, but not one hour, produce marked decreases in enzyme activity which are evident when the tissue is subsequently incubated in oxygen.

All of these experiments were designed to test the maximal activity of the enzyme systems involved. An excess of substrate was provided in each experiment so that the activity of the cell enzymes, and not the concentration of substrate, would be the rate-limiting factor. The object of the experiments was to measure the activity of these enzyme systems under aerobic and anaerobic conditions. The results provide us with an estimate of the upper limit of the metabolic activity of the tissue but they do not provide an estimate of the rate of metabolism *in vivo*.

It is conceivable that the differences between young and term fetal tissues observed in the rat, human and goat represent a physiologic adaptation to persistent tissue hypoxia in the latter part of gestation, which is evident as changes in the amount or activity of the enzymes of the glycolytic cycle and perhaps of other enzymes as well. This may be correlated with several reports in the literature that the oxygen saturation of human fetal blood is less at term than in the previous month. If the oxygen tension in the tissues were low for a prolonged period of time, the fetal tissues might undergo

enzymatic adaptations which would provide more energy without utilizing oxygen. After birth, when the tissues are well oxygenated, this enzymatic adaptation would be reversed and the pattern of metabolism would rapidly change to that characteristic of the adult. Such changes in metabolism are indeed evident within 18 hours after birth in the rat.

An adaptive increase in the activity or amount of an enzyme usually occurs in response to an increased concentration of its substrate. The enzyme adaptations postulated here in fetal tissues would presumably occur not because of the lack of oxygen *per se* but in response to an increased concentration of the substrate of the enzyme involved. The accumulation of intermediates in the glycolytic cycle would occur in hypoxia and this would lead secondarily to an adaptive increase in enzyme activity. As the increasing hypoxia required the tissue to meet more of its energy requirements by glycolysis, and possibly by other energy-yielding reactions which can proceed in the absence of molecular oxygen, the concentration of the substrate of the rate-limiting enzyme would increase. This would lead to an adaptive increase in the amount or activity of the rate-limiting enzyme.

Our experiments have shown that lipogenesis can be of no significance in the ability of the fetus to withstand hypoxia. Under anaerobic conditions, glycolysis is increased four-fold but lipogenesis is decreased to one-tenth the aerobic rate. It would appear that the remarkable resistance of the mature fetus and newborn to hypoxia is not the result of some single metabolic change but is the result of a combination of several, perhaps many, alterations in metabolic patterns, each of which adds a small amount to the energy economy of the fetus. Added together, these metabolic adaptations provide a considerable measure of safety to the fetus as it undergoes the hypoxia of the birth process.

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Columbia University, Presbyterian Medical Center,
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Acidosis of the Newborn and its Relation to Birth Asphyxia[1]

by L. STANLEY JAMES, M.B., New Zealand[2]

Oxygen levels in the newborn infant at delivery have been intensively studied in recent years, blood being obtained from the umbilical cord (4, 9, 15, 17, 30, 32, 35). These studies have revealed a wide range of values. Eastman (9) was responsible for some of the earliest pioneering work. He reported oxygen saturations in the umbilical artery from 6 to 27 per cent, and in the vein 38 to 58 per cent, in 15 babies delivered vaginally. In one elective cesarean section a value of 30 per cent was obtained from the umbilical artery and 63 per cent from the vein. Table 1 demonstrates that the larger the series, the wider has been the range. The present study shows 0–67 in the artery and 9 to 96 in the vein. A few samples from the umbilical vein have been almost identical to maternal arterial blood. It was futher observed that even at elective cesarean section the same wide range was obtained.

Some investigators have taken an average of these values to be an indication of the normal intra-uterine environment; others have ignored the lower values and taken an average of the remaining ones. Treatment of data in this way is responsible for the current idea that the intra-uterine environment is an anoxic one.

However, this method of analysis is valid only when sampling conditions are stable, and the subject is in a steady state. These criteria hardly apply to the birth of the baby being squeezed through the vagina; the cord may be compressed and the strong expulsive contractions of the uterus are likely to interfere with normal circulation through the intervillous space.

In addition, some conclusions have been made, assuming that the umbilical vein blood represents babies' arterial blood and the umbilical artery contains venous blood. This view of the fetal circulation is open to question since Dawes (3) has demonstrated that the blood in the umbilical artery represents the arterial blood of the fetal lambs, and the blood going to the head is little different from that going to the lower part of the body in the rhesus monkey fetus (5). If the birth oxygenation data are reviewed in the light of this knowledge, it is even more difficult to concede that the cord blood represents the intra-

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TABLE 1. *Comparison of oxygen saturation in umbilical cord vessels.*

Author	Average Per Cent Oxygen Saturation		Number of Cases		Range		Delivery
	Artery	Vein	Artery	Vein	Artery	Vein	
Eastman	16	50	15	15	6–27	38–58	Vaginal vertex
	30	63	1	1			Cesarean section
Smith	16	51	37	40	2–48	16–81	Vaginal vertex
Clemetson & Churchman	31	63	10	12	2–50	35–84	Spontaneous vaginal vertex
Walker	20	48	9	10	1–28	13–60	Spontaneous vaginal vertex
Rooth & Sjöstedt	32	61	69	98	0–62	9–83	Spontaneous vaginal vertex
Present Study	23	51	304	360	0–67	9–96	Cesarean section and vaginal vertex; all vigorous at birth

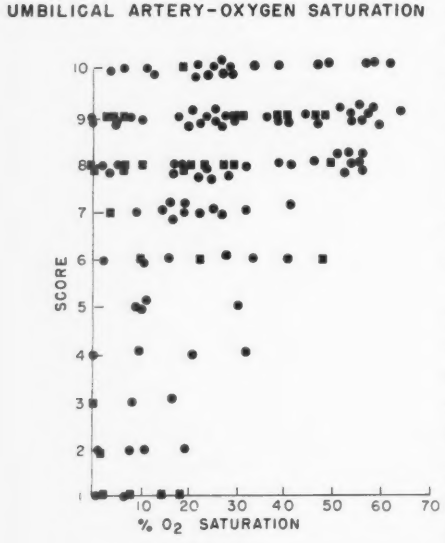


Fig. 1.

uterine environment; otherwise some infants would have to thrive on almost no oxygen.

By correlating the clinical condition of the infant at birth with oxygen saturation, several interesting relationships are seen (Fig. 1). Clinical status may be graded according to the Apgar score (1), by ascribing a number, 0, 1 or 2, to each of 5 readily observable signs: color, respiration, tone, response to stimuli, and heart rate. Vigorous babies then score 7–10, crying within seconds of delivery and maintaining rhythmical respirations by one minute. Depressed infants—limp, unresponsive and cyanotic or pale, with slow heart rates, are in the low score group.

Vigorous infants demonstrate a wide range of oxygenation, some crying lustily with no measurable oxygen in their arterial blood. On the other hand, higher values are not seen in the depressed group. The occurrence of no measurable oxygen in a proportion of vigorous infants, is probably the most weighty evidence against cord blood reflecting the normal intrauterine environment.

An alternative method of analysis is to consider the wide range of values obtained, as reflecting various degrees of interference with exchange of oxygen between mother and baby during the delivery process. This provides a rather different picture. It suggests that the highest values of oxygen in the cord blood more nearly represent the normal in utero en-

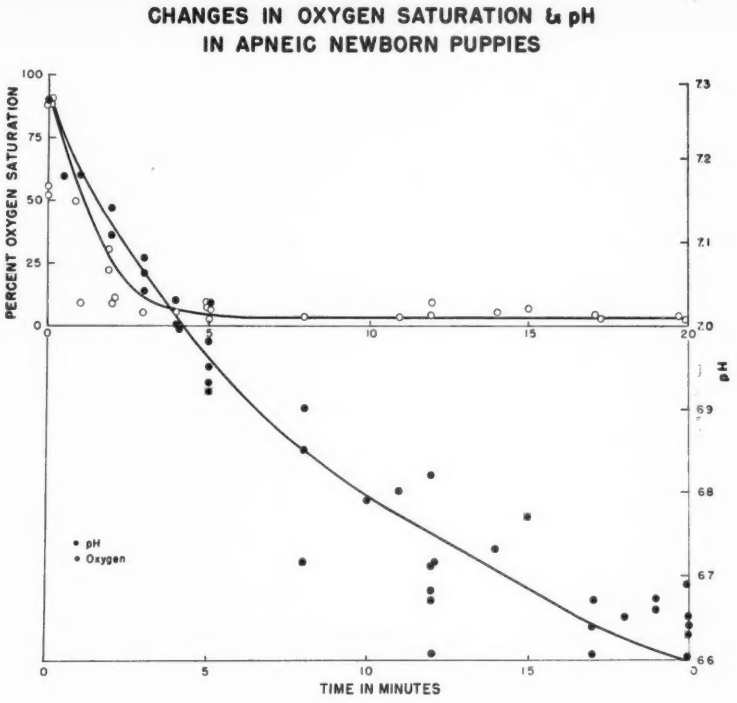


Fig. 2.

vironment. It suggests further, that the large number of low values at birth indicate that the baby is born with his oxygen reserves exhausted.

Acidosis and Asphyxia

These levels raise the question of just how long the infant has been anoxic. Studies in adult dogs indicate that oxygen saturation will fall to below 10 per cent in only three minutes of apnea (11), and in human adults, a fall to 20 per cent occurs in two and a half minutes (20). Serial determinations in apneic newborn babies, give little information about the rate of fall of oxygen saturation since levels are already so low. However, the rate of change has been studied in newborn puppies delivered by cesarean section. Figure 2 demonstrates that oxygen saturation falls from over 90 per cent to less than 10 per cent in approximately 2 minutes.

This figure also demonstrates that if exchange of oxygen is prevented, there are changes in addition to the fall in oxygen saturation. Carbon dioxide accumulates and pH falls rapidly, averaging. 0.1 of a pH unit/minute for the first 5 minutes and then approximately 0.1 of a pH unit every 3 minutes. These results are similar to those observed by Dawes in newborn lambs (5). It will be demonstrated later

that the human infant behaves in a similar fashion.

A horizontal line has been drawn at a level of pH 7.0 and zero oxygen. This is the point where adult animals develop ventricular fibrillation and die. However, puppies continue to have a good heart beat and blood pressure, and the pH continues to fall to levels which are not seen in adult medicine.

The pH change occurs not only as a result of the accumulation of carbon dioxide, but also of fixed acid radicals such as phosphate and lactate. Carbon dioxide tension rises at the rate of 5–10 mm Hg per minute and the buffer base[1] initially falls about 2 milliequivalents per liter per minute. Therefore, in the absence of respiration, not only does the oxygen level fall precipitously, but a profound acidosis also occurs, which is contributed to by carbon dioxide and other metabolic acid products. These collective changes have been defined physiologically, as asphyxia. Thus asphyxia includes anoxia, carbon dioxide retention, an acidosis and other biochemical changes to be discussed below.

Appreciation of the rate at which oxygen saturation and pH can change, emphasizes how a brief period of cord compression, or alteration in the uterine circulation could change these factors, and offers an explanation for the low levels of oxygen which are found in many vigorous newborn infants.

If the low levels of oxygen in the newborn baby reflect a period of deprivation or reduced exchange of oxygen with the mother, changes in carbon dioxide tension, pH and buffer base should also be present. These concurrent changes do occur. Blood samples for analysis of oxygen, CO_2, pH, organic acids and electrolytes were obtained from the umbilical artery at delivery, and serially from the infant over the next hour, by means of a soft polyethylene catheter inserted into the umbilical artery, within 1 to 2 minutes of birth.

Values for buffer base in the cord blood (Figure 3) averaged 42 meq/liter in vigorous infants and was significantly lower in the low score group. These levels are somewhat lower than are observed in normal adults, although the highest values are within normal range. A fall in buffer base of 4 milliequivalents could occur in approximately 2 minutes (the same time it takes for the oxygen saturation to fall to 10 per cent). Following delivery a further fall in buffer base occurred in both vigorous and depressed infants, the fall being greater in the depressed group, particularly if resuscitation was delayed. The fall in the vigorous group occurred uniformly and was unexpected, taking place even though the onset of respiration was prompt, i.e. within seconds of delivery. The subsequent rise in the buffering capacity appeared to depend primarily on the effectiveness of respiration. By one hour, levels which were similar to the maternal level before labor began were attained, the average rate of recovery being similar in vigorous and depressed infants.

A similar pattern of change occurred in the tension of carbon dioxide and in the levels of lactic acid, but was a mirror image of the changes in buffering capacity

[1] Buffer base (31) refers to the amount of available buffer, both bicarbonate and protein of plasma, and hemoglobin. The value for normal males is 47 milliequivalents per liter and for pregnant women 42 milliequivalents per liter. A depression of the buffer base is a measure of metabolic acidosis.

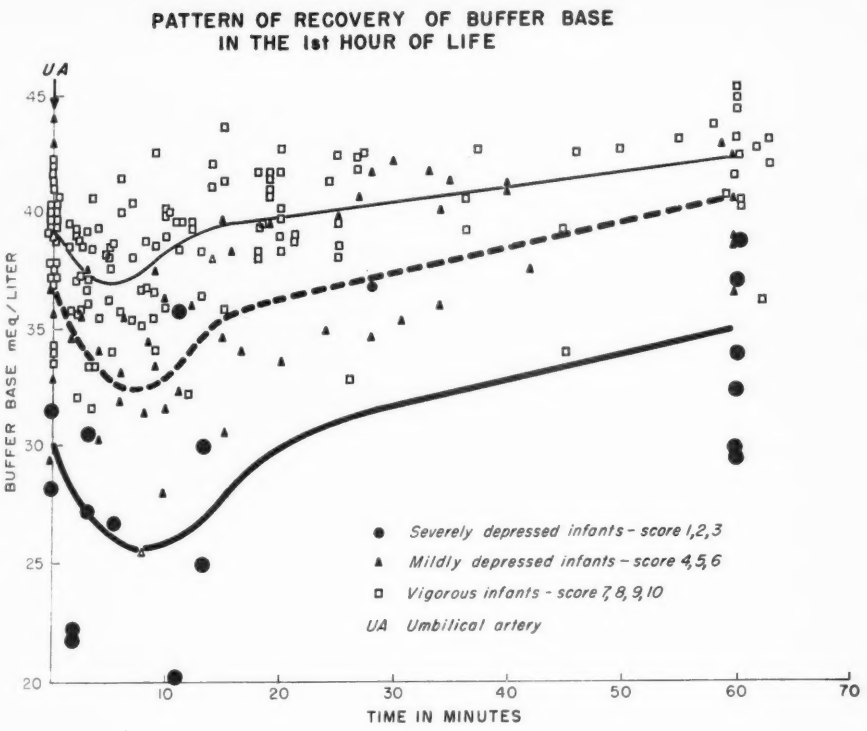


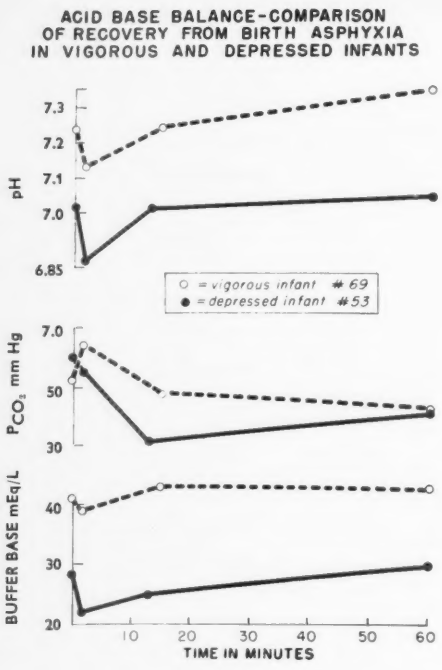
Fig. 3.

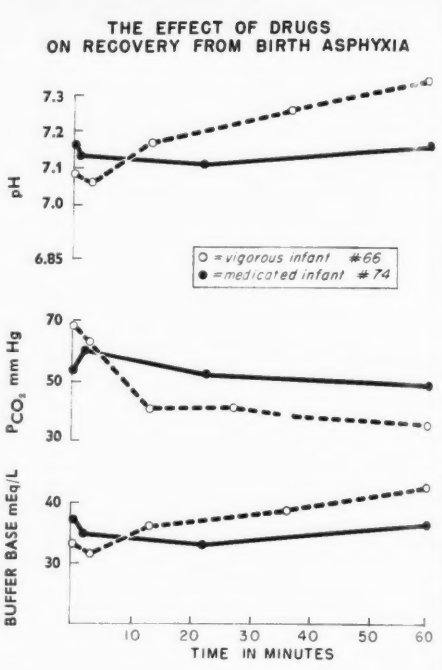
(i.e. there was a brief rise in Pco_2 and lactic acid, and then a subsequent fall). The lactic acid levels acount for approximately half to two thirds of the change in buffer base.

These data demonstrate that an increase in acidosis following delivery takes place even though vigorous respirations start immediately the baby is born. This is unlikely to be due to muscular movement since a greater rise is seen in the limp unresponsive infants who require resuscitation. It is probably due to two factors: first, re-establishment of blood flow in areas that have been poorly circulated; second, an unloading of acid products of metabolism, accumulating during a period of oxygen deprivation. A similar rise is seen in seals when they surface after diving. Thus, this brief increase in acidosis following birth, is added evidence of an anoxic period during the final stages of delivery. It further implies that the cord blood may not truly reflect conditions within the infant.

Acidosis and Potassium Levels

Acidosis is reflected in the potassium levels. Here the depressed infants have values which average one milliequivalent higher than the vigorous group. Over the





Figs. 4–5.

first hour, with recovery from birth asphyxia, the values fell by approximately one milliequivalent per liter, the vigorous infants reaching the mean maternal arterial levels by this time. Occasionally potassium levels in the cord blood may be as high as 10 milliequivalents per liter. In the present study such values have accompanied severe asphyxia associated with some form of cord occlusion. Three infants studied have had abnormally elevated levels at one hour. One of these was an edematous infant of a diabetic mother, in respiratory distress, the others were severely asphyxiated due to diaphragmatic hernias and hypoplastic lungs.

These high values stimulated a study of the rate of rise of potassium in the placenta after the birth of the baby. This appears to occur quite rapidly and correlates with a fall in pH. The rise in potassium was due to a transfer from within the cells and not hemolysis since the plasma hemoglobin was not elevated in any of the samples accepted for analysis. In obtaining these results, care was taken to remove a large volume of blood from the placental vessels, in order that blood from within the villi could be obtained and not just a sample from the superficial veins.

These studies have demonstrated that potassium levels in vigorous infants, who achieve a relatively normal acid-base balance by one hour are little different

from those of the adult, irrespective of the gestational age. This confirms recent studies that potassium levels are not elevated in normal prematures (8, 13, 18). High values may be the result of acidosis or disturbances in acid-base balance; or because the samples were obtained from the placenta some time after birth (36).

Factors Which May Depress an Infant at Birth

Asphyxia

A comparison of individual babies serves to emphasize some of the details which are lost when averages are taken. Figure 4 shows the pattern of change in pH, CO_2 tension and buffer base in a vigorous infant (dotted lines) delivered after an easy and uncomplicated labor of a multiparous mother who had not been given analgesia or anesthesia; this is compared with a severely asphyxiated infant (continuous line) who was born under regional anesthesia following signs of fetal distress, bathed in thick meconium, and with the umbilical cord wrapped 3 times round his neck. At delivery he was completely limp and unresponsive. Following intubation and artificial expansion of the lungs, the first breath occurred at $3\frac{1}{2}$ minutes, and deep, well sustained respirations continued thereafter. The carbon dioxide tension fell rapidly, but the metabolic acidosis showed a much slower rate of recovery.

Medication

Figure 5 compares an infant delivered with no medication (dotted line) with an infant whose mother was given 200 mgm of barbiturate and 100 mgm of demerol over three hours, prior to delivery (continuous line). Both infants were in the vigorous group and breathed spontaneously within seconds of delivery. Here again the difference in rate of recovery is unmistakable, the elevated carbon dioxide tension being evidence of hypoventilation in the medicated infant.

Figure 6 indicates the degree of change when the onset of respiration is a little irregular. The infant whose mother received a variety of drugs (demerol 100 mgm. seconal 200 mgm. and thorazine), represented by a continuous line, is again compared to an infant delivered with no medication. At birth he was in the mildly depressed group being given a score of 6. Although he breathed spontaneously within 20 seconds, the respirations were not regular and he remained cyanotic and somewhat limp. The pH fell rapidly to below 6.9, carbon dioxide tension rose and buffer base was depressed. With gentle stimulation and added oxygen these changes were readily reversed.

Trauma of Labor and Delivery

The infant in Figure 7 falls into a completely different category—a precipitous delivery. The cervix dilated fully within 30 minutes of the onset of labor. The mother received no medication or anesthesia. At delivery the infant (continuous line) appeared to be in satisfactory condition, but comparison of his recovery pattern with an infant delivered after an easy labor (dotted line) shows a difference.

These examples illustrate that the clinical condition of the infant at birth and his biochemical readjustment are influenced not only by the dose of anesthetic agent, but also by the degree of biochemical

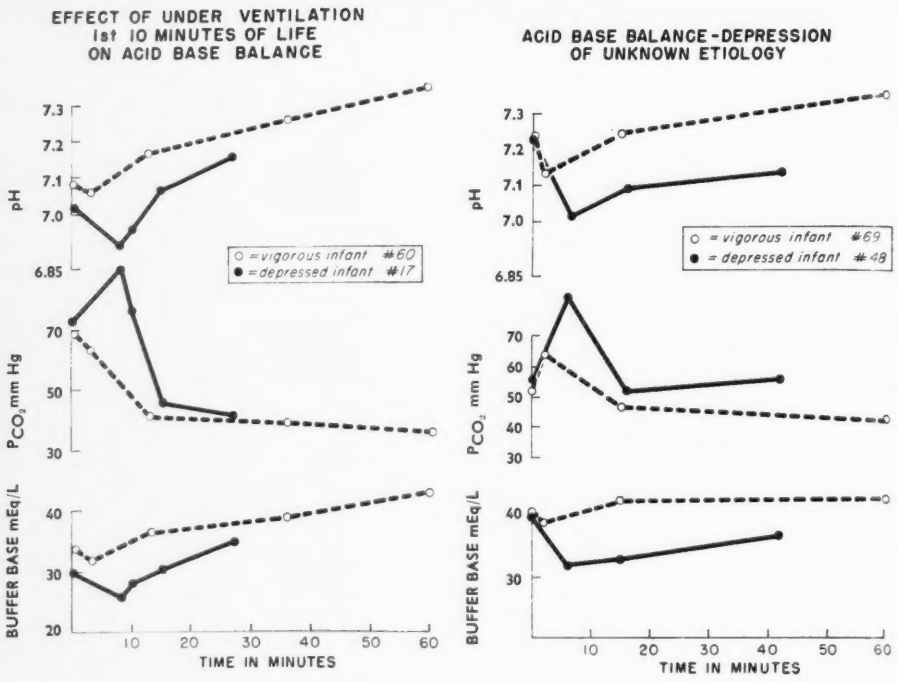


Fig. 6–7.

change itself, and a third factor which is difficult to define—relating to the physical trauma of delivery. All three must be taken into account in evaluating the infant and particularly his response to medication. The presence of two unknown variables, namely the biochemical changes of birth asphyxia and delivery trauma, undoubtedly account for the poor correlation so frequently found between the dose of a particular drug, and the response of the infant, when he is born.

Oxygen saturation rises rapidly, and within minutes of birth is over 90 per cent in vigorous newborns, and also in the depressed group if efficient resuscitation is given. However, the acidosis remains and disappears at a slower rate. These observations not only reveal the extreme lability of oxygen levels, but suggest that the degree of acidosis is a truer indication of a period of oxygen deprivation.

In summary—the wide range of oxygen saturation values,—the relationship between these and other variables which change with asphyxia, namely carbon dioxide tension, acidosis and potassium levels,—and the pattern of recovery following birth all suggest that during the delivery process, there is a marked reduction in exchange of oxygen and carbon dioxide between mother and baby.

Effect of Oxygen to the Mother during Labor

If this circumstantial evidence is true there should be little difference in the oxygen saturation of the infant, when the mother is given added oxygen. A group of 40 infants delivered with the mothers breathing air, were compared to a group of 40 infants where the mother was given pure oxygen for up to one hour before delivery. There appeared to be no significant difference between the two groups (18). This is contrary to several published reports (7, 19, 23, 24, 28), but these have been based on small numbers of cases—usually less than 15 and sometimes only 5. When the normal range of variation is so great, conclusions can only be drawn, if a larger number of babies are studied.

While there can be little question that increasing the oxygen tension gradient across the placenta will result in an increased transfer to the fetus, for this to occur the maternal-placental-fetal circulations must be intact and functioning efficiently. The result of this study in no way alters the rationale for giving oxygen to the mother, but emphasizes that the effectiveness of this procedure during delivery, or fetal distress, deserves further study, particularly in view of the experimental evidence that high oxygen tensions constrict the fetal vessels in the placenta (21, 27).

Evidence presented suggests that the delivery process is primarily responsible for the acidosis and low oxygen levels at birth, and that the normal intrauterine environment may be much less anoxic than is currently believed. The infant appears to survive this episode of asphyxia. With good ventilation, a vigorous non-medicated baby will have a relatively normal acid-base balance by one hour.

Anaerobic Respiration

Questions as to how much anaerobic respiration is carried out before birth, or why infants can survive a much longer period of asphyxia than an adult, remain to be considered.

Referring again to the apneic newborn puppies, (Fig. 2), it may be seen that although the oxygen saturation falls to below 10 per cent within two minutes—and the pH falls rapidly, the puppies continued to live. The way in which the pH continues to fall indicates that acid products (mainly lactic) are accumulating, and that these acid products are not being metabolized at an appreciable rate by any known or unknown metabolic pathway.

Just why the newborn heart continues to function under these severe conditions of anoxia and acidosis is an interesting question. Dawes (6) has suggested that this ability resides in the stores of glycogen within the heart muscle, the more immature the animal, the greater the amount of glycogen, and the longer the period of survival under anaerobic conditions.

In a brilliant series of experiments, using radio-tagged isotopes and pregnant monkeys, Plentl (10) and associates have recently demonstrated that lactic acid and carbon dioxide pass rapidly from mother to fetus or from fetus to mother. And further that the fetus metabolizes lactic acid to carbon dioxide as rapidly as the mother.

These studies together with the evidence that the biochemical changes in asphyxiated adult and newborn animals are similar, and occur with equal rapidity, suggest that the metabolism of the fetus

is not unlike that of the adult. Any greater ability to form lactic acid could reside in either enzyme concentration, or the presence of necessary substrate at a particular site.

The rise in maternal lactic acid levels during pregnancy studied by Hendricks (14), at first appeared to provide promising evidence in support of anaerobic metabolism. Unfortunately, this rise does not always occur (34). During labor, lactic acid is extraordinarily variable depending upon the activity of the mother, and during delivery may be influenced by the anesthetic agent as well as maternal activity. Because of these variables, it is doubtful if the maternal levels can ever be taken as a true reflection of the fetal levels and the degree of anaerobic metabolism.

A rise in the concentration of lactic acid dehydrogenase during pregnancy has been reported (12). This might be construed as supportive evidence of increasing anaerobic metabolism. However, Little (22) has failed to confirm this, and even during labor, the majority of normal mothers do not have an increased concentration.

It seems more likely that anaerobic metabolism is present as an emergency mechanism only. The ability of the fetus and newborn to survive prolonged anoxia, may depend not so much on an unusual anaerobic mechanism, but rather on enzyme concentration or increased stores of glycogen in vital areas such as cardiac muscle.

Conclusion

These observations which we have made on babies at birth, not only reveal the extreme lability of oxygen levels but suggest that the degree of acidosis is a truer indicator of a period of oxygen deprivation. The infants with a mild metabolic acidosis at birth may have either a relatively high or an extremely low oxygen saturation. In the absence of excessive medication or anesthesia these infants are always vigorous. On the other hand those infants with a profound metabolic acidosis always have low oxygen levels at birth and are invariably depressed.

From adult and experimental physiology, acidosis may carry important implications (16). It increases the toxic action of potent anesthetic agents (2). Renal function is diminished with a pH of 7.2 and in adults renal shutdown occurs when the pH reaches 7.0 (25, 33). Other effects relate to optimum pH, for various enzyme functions. Finally, cardio-vascular collapse is imminent when the pH falls below 6.9 (26). For those actively engaged in the care of babies at birth, it is important to bear in mind how rapidly the pH will fall in the presence of apnea.

Acknowledgements

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Physiological Aspects of Temperature and Oxygen Effects on Newborn Infants

by PETTER KARLBERG

Before discussing the effects of environmental temperature on the newborn infant, I would like to mention, briefly, the principals of body temperature control.

In homoiotherms the body temperature is kept constant at varying environmental temperatures in two different ways: altering the heat production by changing the metabolism; or altering the heat loss by changing the blood flow to the skin. In a cold environment shivering may be involved, while in a warm environment there may be sweating. For a long time, it has been known that for warm-blooded adult animals, there is a certain environmental temperature range, called the neutral temperature, at which the metabolic rate is minimal. Above this temperature range, the metabolism as assessed from the oxygen consumption, is extremely variable. With a decrease in environmental temperature below the neutral temperature, there is a metabolic increment which is species specific and highly regular. This relationship is well shown in Fig. 1, taken from Herrington's work on adult rats (13). There is a clear metabolic minimum at a certain narrow temperature range. A similar relationship also holds for adult human beings (1).

Owing to the lability of the body temperature of newborn infants, and especially of premature infants (23), it has been discussed for a long time, whether or not the adult type of temperature regulation is already effectively present immediately after birth.

Day has shown that cool air provokes an increase in heat production in premature infants older than one week (10) (Fig. 2). In addition, he found an effective control of heat loss by vasoconstriction.

Recently, Brück has shown that newborn infants, as well as premature infants have a heat regulatory mechanism even within the first hour after birth (4, 5, 6).

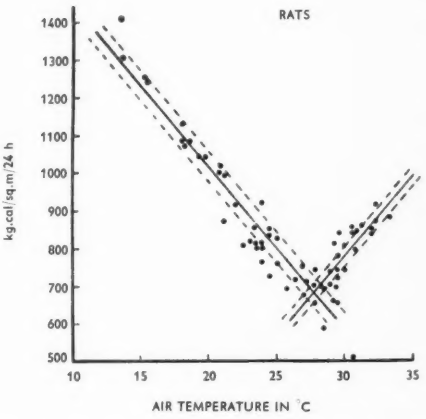

Fig. 1. Standard metabolism of albino rats at various temperatures. Each point represents the mean of 10 animals (Herrington: Am. J. Physiol., *129:* 129, 1940).

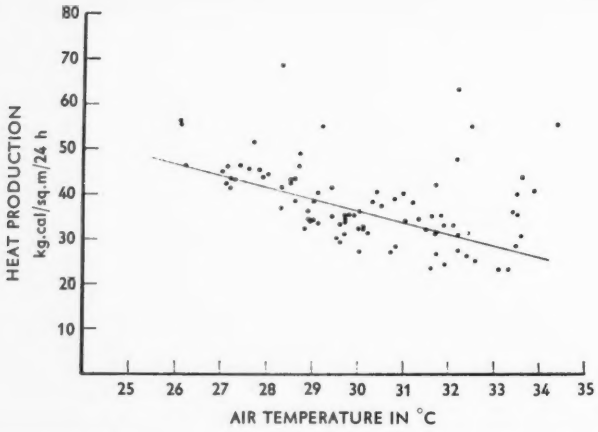

Fig. 2. The relationship between air temperature and the production of heat. In the calculation of the regression line, those periods were omitted in which the infant perspired actively. In infants who perspired, there was a great elevation of heat production due to hard crying. These periods are indicated by open circles (Day: Am. J. Dis. Child., *65:* 376, 1943).

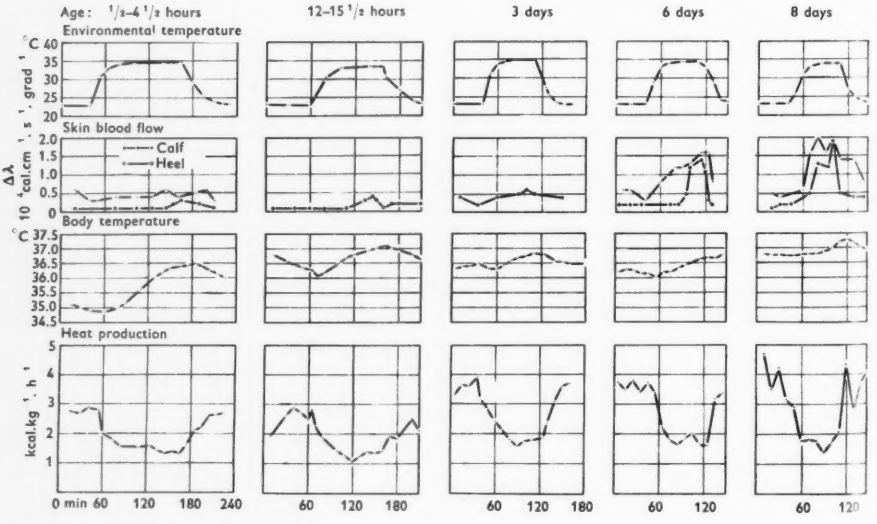

Fig. 3. A series of 3–4 hours' studies in a full-term newborn infant at various times after birth, 1/2–4 1/2 hrs, 12–15 1/2 hrs, 3 days, 6 days and 8 days. The top row shows changes in environmental temperature; the second row, skin blood flow; the third row, body temperature; and the last row, the heat production (Brück, Brück, Lemtis: Pflügers Arch. ges. Physiol., *267:* 382, 1958).

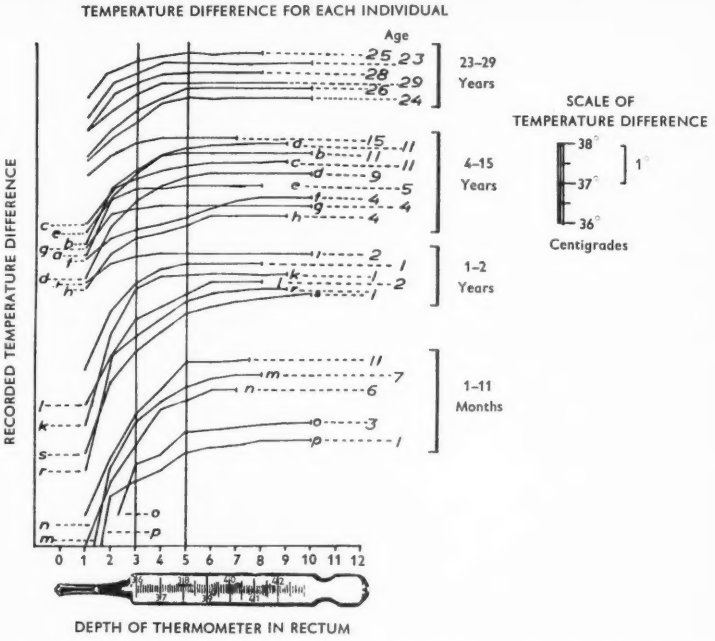

Fig. 4. Differences in recorded rectal temperature at various depths of insertion of the thermometer (Karlberg: Acta Pædiat., *38:* 359, 1949).

Fig. 3 shows one of his studies in a full-term newborn infant, at various times after birth, $^1/_2$–$4^1/_2$ hrs, 12–$15^1/_2$ hrs, 3, 6, 8 days. An increased metabolic rate at a decreased environmental temperature is already present within the first hours after birth, although not to the same high level as some days after birth. Concerning the skin blood flow, there is an effective vasoconstriction at low temperatures. However, the vasodilatation at high temperature is present to any considerable extent only after some days following birth. These responses, the metabolic, as well as the vasomotor, he also found in premature infants.

Thus, it appears that regulatory mechanisms in response to low temperature in newborn infants, as well as in premature infants, are essentially the same as in the adult. The main cause of lability of the temperature seems to be the fact that the relationship between the heat-losing surface of the body and the heat-producing body mass is approximately $2^1/_2$ times greater in newborn infants than in adults (23). This ratio may be increased to as much as $3^1/_2$ times in premature infants. This is the main reason why the neutral environmental temperature is inversely related to the body size.

The relationship between surface area and body mass leads to another phenomenon, important in the clinical assessment

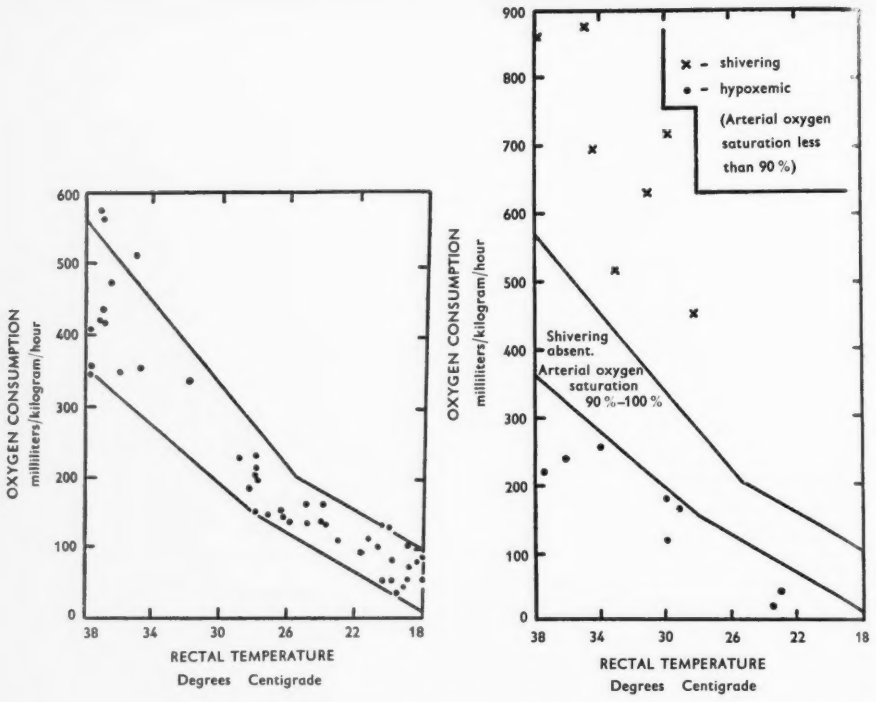

Fig. 5*a*. Scatter graph of all oxygen consumption findings during cooling. Shivering was controlled and arterial oxygen saturation was maintained at 90 % to 100 % in the experiment.
b. Graphic illustration of effects of shivering and developing hypoxaemia upon oxygen consumption. This graph is drawn to the same scale as figure *a*. The lined area is identical with zone outlined in figure *a* (Bigelow, Lindsay, Harrison, Gordon, Greenwood: Am. J. Physiol., *160:* 125, 1950).

of the body temperature in the neonatal period. The difference between the rectal temperature taken at 3 cm depth and deeper levels is greater in newborn infants than in adults and older children and also greater in prematures than in full-terms. (see Fig. 4) (15). This indicates a more rapid heat diffusion from the deeper parts of the body towards the periphery. As the rectal temperature routinely is taken at a maximum depth of 3 cms, an observed temperature of 36° in a premature will not necessarily indicate a true condition of hypothermia, and this phenomenon should be taken into consideration especially in the case of premature infants.

An increased metabolic rate in response to a decrease in environmental temperature is, therefore, present in the first week as it is later in life. This is true for normal individuals. However, this response will not always be found under abnormal conditions. This is so under anesthesia, as is shown in Fig. 5*a* taken from Bigelow's work on dogs (2). In this situation, the dogs responded to a decreasing environ-

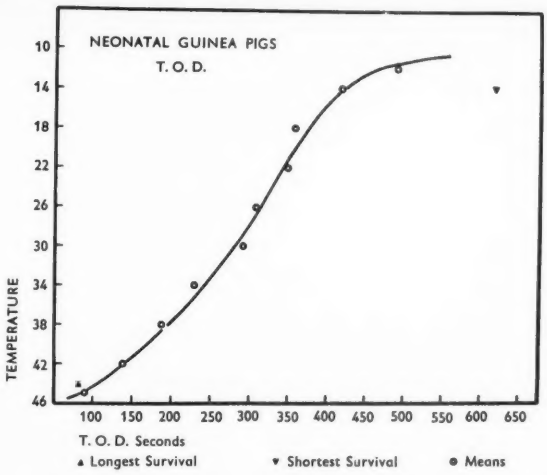

Fig. 6. The times of death of 205 neonatal guinea pigs exposed to 95 per cent $N_2 + 5$ per cent CO_2 at different temperatures (Miller: Neurological and psychological deficits of asphyxia neonatorum, Ed. by William W. Windle, Ph.D., Charles C. Thomas, Springfield, Ill., p. 105).

mental temperature like poikilothermic animals, in that they failed to increase their metabolism and to shiver, and their body temperature decreased. Under the conditions of these experiments, a tissue oxygen deficit did not develop during the period of cooling. However, the graph b in Fig. 5 illustrates that in cases with developing hypoxemia, there is an even lower metabolism in relation to the body temperature. This sort of experimental observation makes it clear that the oxygen tension in the tissues is an important factor in temperature regulation.

It has been known for a long time that the survival time of severely hypoxic newborn animals is increased at a lowered body temperature, as is shown in Fig. 6 taken from Miller (19).

Recently, Westin, Miller and collaborators have reported 6 cases of severely hypoxic newborn infants that were subjected to rapid cooling within some minutes after birth until their body temperature was between 30 and 23 degrees centigrade (see Fig. 7) (25). These infants started to breathe spontaneously within 14–79 minutes after birth. They were at the same time given gastric and intestinal oxygen and 3 of the 6 cases were also given oxygenated blood through the umbilical vein. One of the cases died after 30 hrs. The others survived and seemed to develop normally during a follow-up period of some months. This suggests that deep hypothermia affords some protection against damage from severe hypoxia in human beings, as well as in animals. This deep hypothermic treatment must be investigated further, especially with respect to the type of situation in which it should be used. The treatment of severely hypoxic newborn infants by deep rapid hypothermia should be regar-

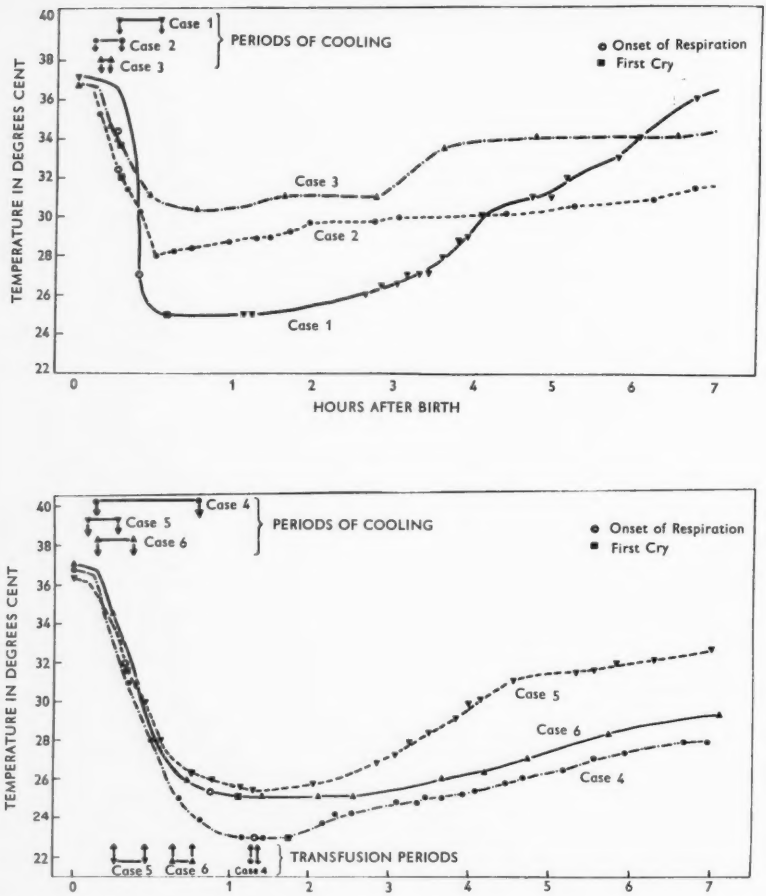

Fig. 7. The upper diagram: Records of Cases 1, 2 and 3 showing periods of cooling and time and temperature of the onset of breathing and first cry.
The lower diagram: Records of Cases 1, 5 and 6 showing period of cooling and transfusion of oxygenated blood and the time and temperature of onset of breathing and first cry (Westin, Miller, Nyberg, Wedenberg: Surgery, *45:* 868, 1959).

ded more as a kind of resuscitation at birth rather than as a method of treating infants during the newborn period.

The observation of animals during hypothermia and hypoxia led Silverman to make the clinically important test as to whether hypothermia would serve effectively to protect the premature infant against the effects of the hypoxia which so often develops in such infants, during the neonatal period (21). However, the hypothermic group, whose body temperature was kept about two degrees lower than the normal control group, instead

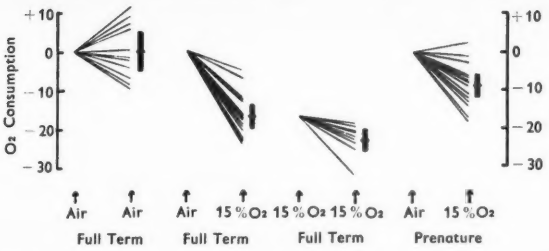

Fig. 8. Percentage changes in O_2 consumption of term and premature infants while breathing O_2 at concentrations of 20 or 15 %. Note the fall in O_2 consumption following administration of 15 % O_2. The vertical solid bar represents the standard deviation by the mean (Cross, Tizard, Trythall: Acta Pædiat., *47:* 217, 1958).

of showing the expected increase in survival rate, actually showed a decrease. Thus, mild hypothermia in primarily normal prematures does not seem to be clinically beneficial.

Cross, Tizard, Trythall have studied the effect of hypoxia in newborn infants and found a significant decrease in oxygen consumption after 5 minutes of breathing 15 % oxygen (see Fig. 8) (9). Brodie, Cross and Lower have found that the body heat production dropped significantly, when the oxygen intake was reduced by placing the infants in a 15 % oxygen atmosphere (3). However, June Hill has repeated these studies in newborn kittens and has shown that the decreased oxygen consumption with decreased body temperature does take place in 15 % oxygen atmosphere, but only at a lowered environmental temperature (14). Within the range of neutral temperature, there was no metabolic change and no body temperature change. The interesting observations of Cross and his co-workers on human infants should, thus, be considered at other environmental and body temperatures, a fact which has been pointed out by Cross himself (8).

As we understand it at the present time, it seems that lowering of the environmental temperature for the purpose of decreasing the demand on an impaired lung function, will only be effective in hypoxic newborn infants.

Some of our own observations in this field have indicated this as well (17). In premature infants with severe pulmonary atelectasis and inadequate oxygenation of the blood, a lowered environmental temperature resulted in a lowered body temperature and a lowered respiratory rate, which was taken as an indication of decreased demand on the lung function. In cases of respiratory distress but still with adequate oxygenation of the blood, a lowered temperature has resulted in shivering and an increased metabolic rate (16).

This brings up the question—what is hypoxaemia in a newborn or premature infant? The conditions before birth have then to be considered, i.e. in a normal term fetus. Fig. 9, taken from Rooth and Sjöstedt's determinations (20) shows the stepwise decrease in oxygen tension down to the fetal tissue value of about 10 mm Hg as determined from the amniotic

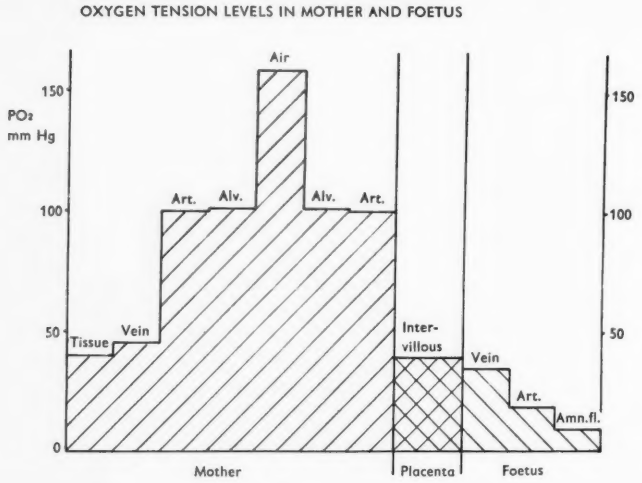

Fig. 9. Oxygen tension levels in mother and foetus (Rooth, Sjöstedt: unpublished data, which have kindly been placed at my disposal).

fluid. This is much lower than the oxygen tension in the tissues in extra-uterine life, which is represented by the mother's value of about 40 mm Hg. A normal newborn infant emerging into the atmosphere and breathing the 21 % oxygen in the air will thus have potentially a considerable increase in the oxygen tension of its tissues.

However, an increased oxygen tension may lead to blood vessel reactions. Under certain circumstances such a reaction causes retrolental fibroplasia in premature infants (18). Present studies by Gyllensten show that similar vessel changes occur in the brain of newborn rats exposed to high oxygen concentrations (12). Cedergren, Gyllensten and Wersäll have also further studied the formation of hyaline membranes in the lungs under similar circumstances (7). Our own investigations have shown that an increased concentration of oxygen in the inspired air may change the elastic properties of the lungs, as determined by measurements of the lung compliance in infants a few days after birth (24). This indicates that several hours' exposure to an increased oxygen concentration may affect the function of the lungs.

Normal newborn infants adjust to the sudden increase in oxygen tension from fetal life to extra-uterine life with air breathing without serious difficulty. However, if the pregnancy ends with a considerable hypoxia of the fetus the extra-uterine air breathing will cause a much more marked and sudden oxygen increase which may involve significant difficulties in adaptation of the newborn infant. Sjöstedt and Rooth's approach to the neonatal care, especially of the premature infants, of keeping them in 15 % oxygen (22) during the whole neonatal period,

seems therefore reasonable. They have reported together with Engleson this procedure, used on about 25 premature infants, with good results. These cases also showed a mild hypothermia, which is important (11).

It may be that the combination of 15 % oxygen and a mildly lowered environmental temperature is a valuable method for carrying newborn infants, especially the premature infants through the risky postnatal period. However, such a method needs further study before it can be put into general use.

Temperature and oxygen are two factors of great importance in the care of the newborn infant. Even though our knowledge is limited a great deal, it is evident that these two factors are interrelated and simultaneous adjustment of temperature and oxygen must be considered. However, other factors, which certainly have to be considered are brought to mind in this connection, for example hypercapnea, but time does not permit further discussions.

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Changes in the Circulation and Lungs at Birth

by JOHN LIND[1]

It is well known that William Harvey in 1628 gave the first exposition of the circulation of the blood in the adult (12). Noteworthy, but perhaps less well known is the fact that Harvey in his splendid treatise clearly described the foetal circulation. He realized that in the foetus the two ventricles work in parallel instead of in series as in adults. He also recognized the significance of the foramen ovale and the ductus arteriosus.

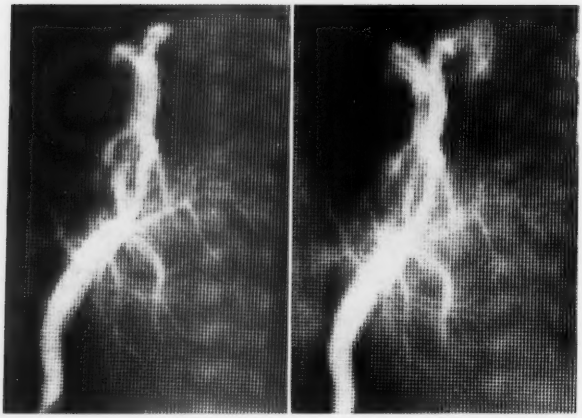
After Harvey, the foetal circulation was for 300 years a matter for speculation and controversy among anatomists. It was not until recently that the experimental methods, which had been used with such success on the adult mammal were first applied to the foetus. In 1927, Huggett (13) showed that it was possible to keep a goat foetus, delivered by Cesarean section and still attached to the mother, in good condition without a significant disturbance of the placental circulation. He observed that the oxygen content of the carotid arterial blood was greater than that of the umbilical arterial blood, thus confirming Sabatier's hypothesis (24). According to this a crossing of the blood streams (i.e. one from the placenta well oxygenated, and the others from the inferior vena cava and the coronary veins) takes place in the right atrium without a significant mixing. Huggett's method was applied to sheep by Barcroft and his colleagues with considerable success (4). In cooperation with Barclay, Franklin and Pritchard (3), they performed the first direct objective recording of the course of the foetal circulation in the intact sheep foetus delivered near term by Cesarean section.

Among the most interesting features of the investigation carried out by Barclay *et al.* was the direct proof that the stream of the well oxygenated blood, passing from the placenta up the inferior vena cava, divided into a large part which entered the left atrium through the foramen ovale, and a smaller part which flowed on to enter the right atrium. This finding fits in well with the observation made by Huggett.

Lind and Wegelius (20) were able to perform angiocardiography on living human foetuses, obtained at legal abortions, with a body weight of between 50 and 500 grams. The foetuses were delivered by Cesarean section, often with the membranes intact, and the contrast was injected within ½ minute after the removal of the foetus.

It was shown that even in the human

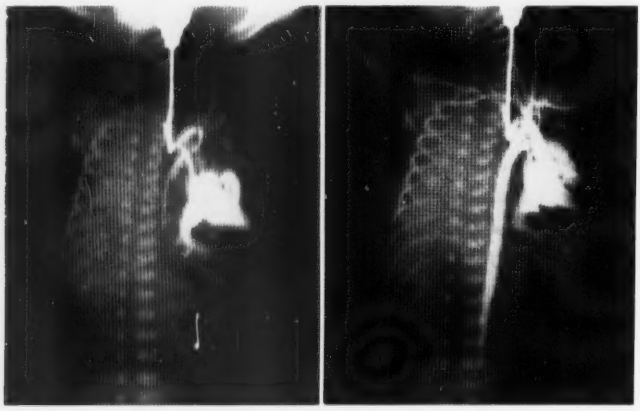
[1] Aided by grants from the Association for the Aid of Crippled Children, New York.



a *b*

Fig. 1. Entrance of the inferior caval blood flow into the foetal heart. Left anterior oblique projection. Injection into the umbilical vein. (*a*) The contrast medium has passed through the ductus venosus and the hepatic veins and fills the inferior vena cava. At the entrance the contrast loaded blood is divided into two streams. (*b*) One tenth of a second later, more blood is directed into the left than into the right atrium.

species most of the placental blood flow is directed to the left side of the heart. The pictures also demonstrate that functionally, the foramen ovale lies between the inferior vena cava and the left atrium. Therefore, it is not necessary to suppose that the two streams of blood cross in the right atrium without mixing (Fig. 1). a theory which has been difficult to understand.



a *b*

Fig. 2. Course of the superior caval blood flow through the foetal heart. Human foetus about 14 weeks old. Right anterior oblique projection. Injection into the internal jugular vein. (*a*) The heart is well contrast filled, the pulmonary conus is clearly seen. (*b*) During the following strong ventricular systole, the aorta, the pulmonary artery, and the ductus arteriosus are well opacified. Almost no contrast medium is seen in the lung vessels.

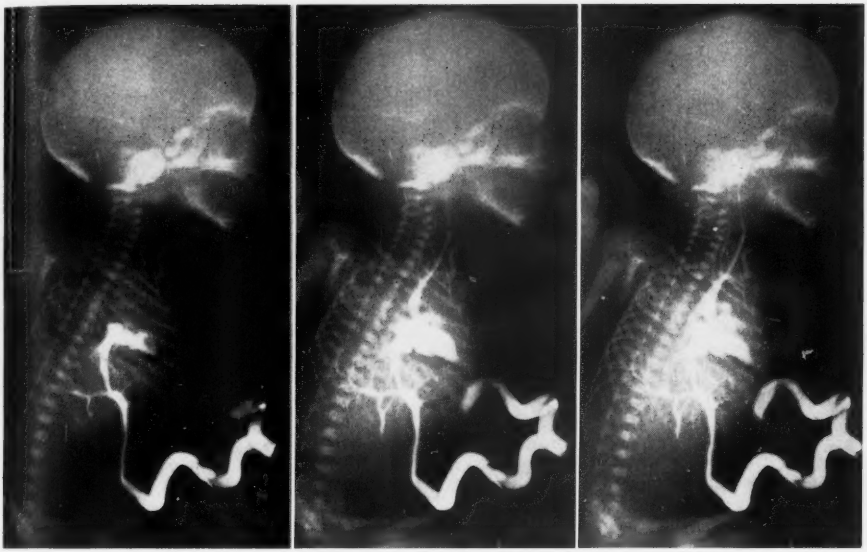


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Fig. 3. Distribution of the umbilical blood flow in the foetal circulation. Human foetus about 20 weeks old. Right anterior oblique projection. Speed of pictures 5/sec. Contrast injection into an umbilical vein. *a*) The contrast medium is passing through the ductus into the foetal heart. *b*) During ventricular systole, the ascending aorta and the innominate artery are well opacified. The descending aorta is not seen. *c*) In the following ventricular systole, the ascending aorta and the branches arising from the aortic arch are clearly seen. The pulmonary artery and the descending aorta are faintly opacified.

Contrast medium entering the heart from the *superior vena cava* could be shown to be limited in its distribution to the right side of the heart. The injection of contrast medium passes out via the pulmonary artery and appears in the descending aorta after being shunted through the ductus. Only traces of contrast medium were seen in the lung vessels. The volume of flow through the lungs is thus small in the human foetus of mid term (Fig. 2).

Dawes and his assistant (8) have done a series of precise studies of the foetal circulation in lambs, using advanced catheterization technique. Such a method has the advantage of enabling a quantitative calculation of the blood flow distribution to be made. Among other interesting data, they showed that 55 per cent of the combined output of both ventricles goes to the placenta which can be regarded as a low resistance circuit placed in parallel with the foetal tissues, both systemic and pulmonary. The foramen ovale and the ductus arteriosus carry 46 and 30 per cent, respectively. Of the foetal total cardiac output, about 12 per cent passes through the lungs which, therefore, offer a high resistance to flow. Dawes did not find any increase in pulmonary blood flow per kg of body weight during the latter part of gestation. Only 15 per cent passes to the forequarters.

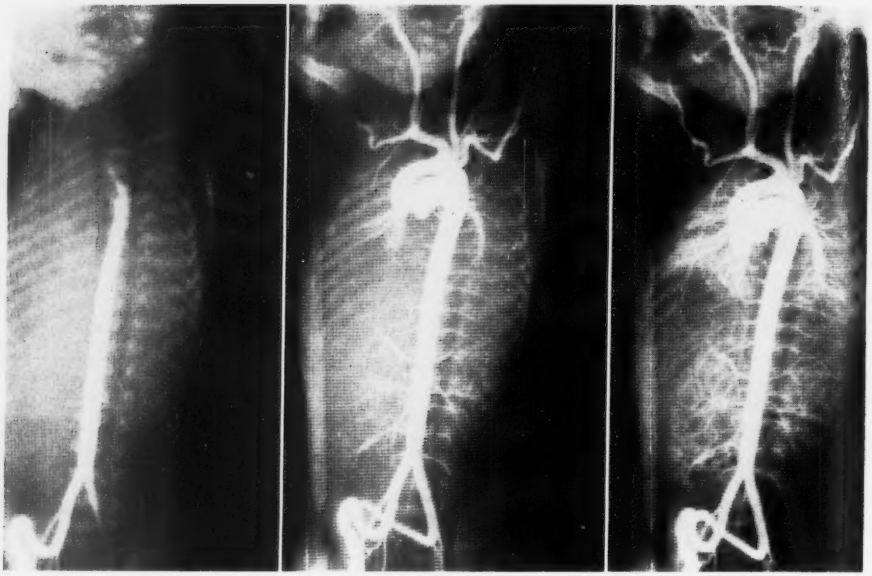

Fig. 4. The relative capacity of the different big arteries in a human foetus, 18–20 weeks old. Retrograde aortography through an umbilical artery immediately after delivery by Cesarean section. Intense contrast filling of the aorta and the vessels originating from the aorta. The large calibre of the coronary arteries and the vessels going to the head of the foetus is striking compared to the small size of the pulmonary artery as well as the renal mesenteria and hepatic arteries. The aorta terminally divides into the two large sized umbilical arteries.

Contrast injection into the umbilical vein of a human foetus, however, gives a striking illustration of the large blood flow to the brain. The cephalic arteries are of impressing calibre and the concentration of contrast medium is higher in these vessels than in the descending aorta, where the dye becomes diluted from the non-opacified blood coming from the pulmonary artery through the ductus. (Most of the blood entering the right ventricle comes from the head.) (Fig. 3.)

A retrograde aortography from a human foetus, 20 weeks of age, gives a rough idea of the capacity of the arterial vascular tree (Fig. 4). One observes that the vessels going to the brain are large, compared to the tiny lung vessels and the very thin renal and intestinal arteries. Therefore, in the human foetus, it seems that more than 12 per cent of the cardiac output goes to the brain. The head of a human foetus is also relatively much larger than the head of a foetal lamb.

Function of the foetal lungs

Opinions regarding an intrauterine function of the foetal lungs are still conflicting. During the last century there has been good evidence that foetal respiratory movements are made in utero. Since the effort required to move fluid through the respiratory tract is quite considerable,

because of the resistance of the narrow passages and the inertia of the fluid mass, it is doubtful whether any significant tidal flow of amniotic fluid occurs. According to Barcroft, foetal respiratory movements in lamb become increasingly difficult to evoke during the later stages of pregnancy, finally appearing only if the foetus is subjected to asphyxia. The presence of meconium and squamous cells in the periphery of the lungs of the infants who have died following intrauterine anoxia, however, indicates that aspiration can occur in the older foetus if the necessary stimulus is applied.

In the rapid transition from intra to extra uterine life which occurs at the time of delivery, the child must, within a very short period of time, establish a lung function adequate for oxygenation of and disposal of carbon dioxide from the blood. Before delivery, there is no real respiratory function of the lungs for puposes of gas exchange.

Whether fluid and electrolytes can be rapidly transferred across foetal lungs is not known. Reynolds (23) showed that when the lungs of a newborn lamb were expanded with fluid it was not absorbed and that the pulmonary arterial pressure remained high. In a series of similar experiments, Dawes (9) has shown that expansion of the lungs with saline caused an increase in pulmonary vascular resistance and a decrease in pulmonary blood flow.

The anatomical status of the lungs just before birth is still not well known. Most authors, however, seem to agree that in the normal foetal development, the lung becomes converted into a complex system of air spaces. Thus, the area of the surface available for respiratory exchange increases much more rapidly than the volume. The characteristic appearance of the alveolus before aeration seems to be that of a crumpled sac (22). The aeration of the lungs thus involves both a replacement of amniotic fluid with air and further expansion of the lung parenchyma.

Fig. 5. Air filling of the upper respiratory passages preceding the first breath. Lateral view. Before the aeration of the lungs, air is seen in the upper airways, in the trachea and the main bronchi.

The most dramatic period in the functional development of the lungs must be from birth to an age of some hours. Serial X-ray examinations of the respiratory changes in the thorax in connection with the aeration of the lungs (14) have shown that even before breathing has commenced, in most cases there is air in the upper airways (Fig. 5). The explanation might be that as a consequence of the compression of the chest wall during birth, fluid is forced out of the lungs to be replaced by air. In addition, it has been possible to demonstrate that the mouth, pharynx and larynx participate in initial air inflation of the lungs (6). Sequential

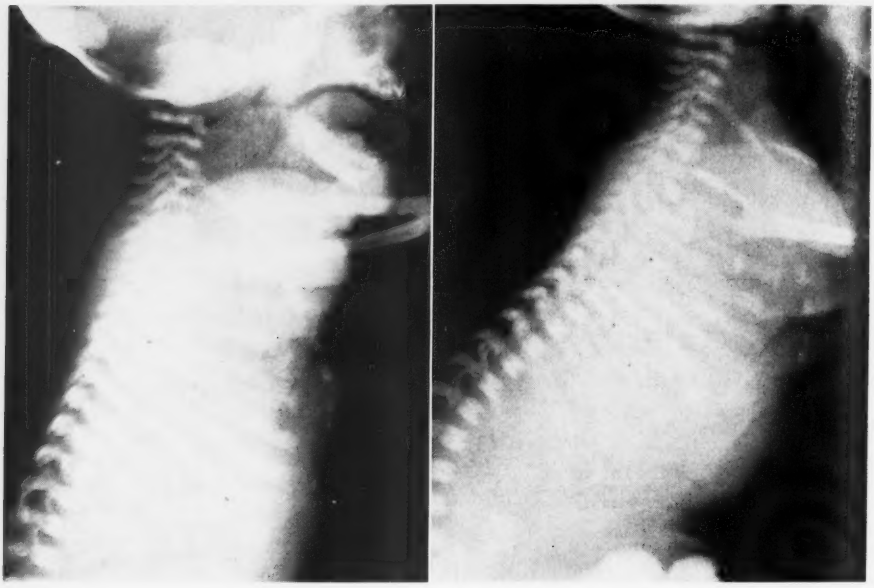

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Fig. 6. Motions of the pharyngeal region preceding initial inflation of the lung of the newborn infant. *a*) At birth, there is a little air seen in the mouth and pharynx. *b*) One third of a sec. later, there is a striking air filling of the pharyngeal region and the pharynx is dilated.

distention and compression of the pharynx cavity before and in association with the first breath have been observed and the successive air filling of the upper respiratory passages is obviously an active process (Fig. 6). In this way, the baby cleans the upper airways from amniotic liquid and mucus which it otherwise would have to draw bakwards into the respiratory tract with the first breath. In some cases, these movements of the pharynx area were similar to those seen in glossopharyngeal respiration. It has been suggested that these movements may prevent egress of air from the lung and thus with an increase in intra-thoracic pressure, prior to expiration, facilitate further distribution of air within the lungs.

At birth, the opaque thoracic cage in the a-p view does not suggest collapsed lungs. The thorax has its typical cylindrical shape with a slight elevation of the ribs even before the first breath. The expansion of the thoracic cavity is brought about mainly by lowering of the floor—the diaphragm—but also by the increasing depth of the thorax (Fig. 7).

The first breath is always accompanied by a more or less marked indrawing of the ribs. The lateral walls of the thorax present a concave shape, most marked just before and during the first part of the inspiration. In some cases, the aeration takes place very easily, and within a third of a second the lungs are roentgenologically well aerated (Fig. 7). In other cases, the

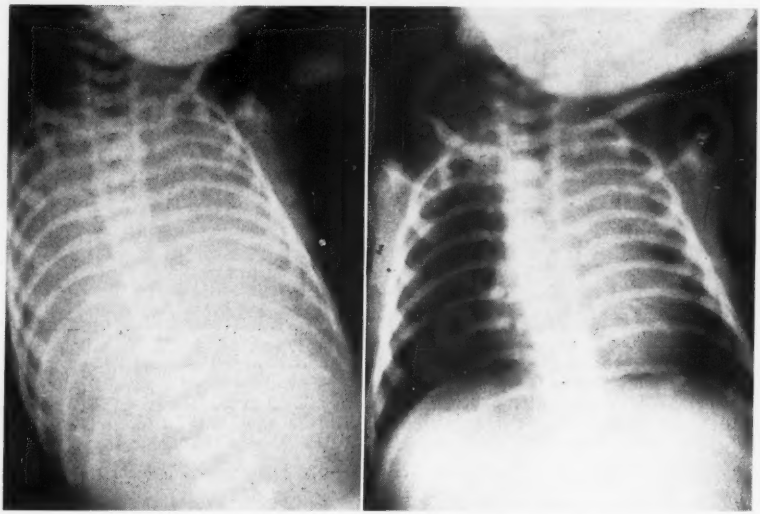

Fig. 7. The baby's first breath. The immediate air filling of the lungs is demonstrated. Birth weight 3300 grams. The opaque thoracic cage does not suggest collapsed lungs. The good air filling of the lungs is not preceded by any significant indrawing of the thoracic wall. The pictures were taken with one third of a second interval.

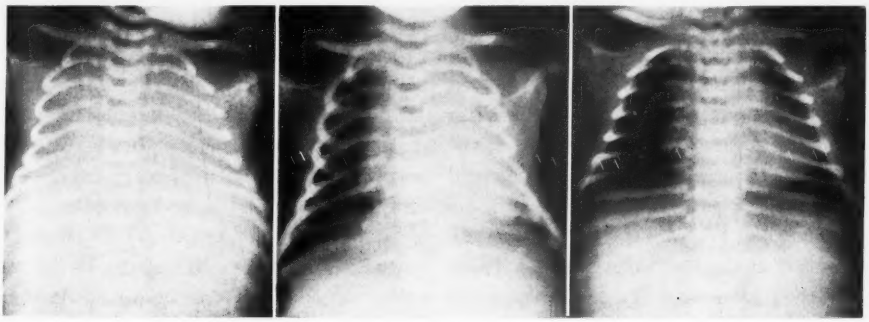

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Fig. 8. The baby's first breath demonstrating the initial inspiratory effort. *a*) As yet, no air is seen in the respiratory tract. *b*) Marked indrawing of the thoracic wall associated with a sudden air filling of the lungs. *c*) In the subsequent expiration there is no great change in the diameter of the thoracic cage compared with a) in spite of the good air filling of the lungs. Note the good aeration of the lungs also during expiration.

successful inspiration is accompanied by a very marked "waisting" and preceded by a series of unsuccessful contractions of the diaphragm (Fig. 8). When the aeration of the lungs occurs, the "waisting" is not seen again to the same extent with subsequent respirations. The amount of residual air in the lungs after the first and the following expirations varies. Following a relatively poor inspiration, there can be

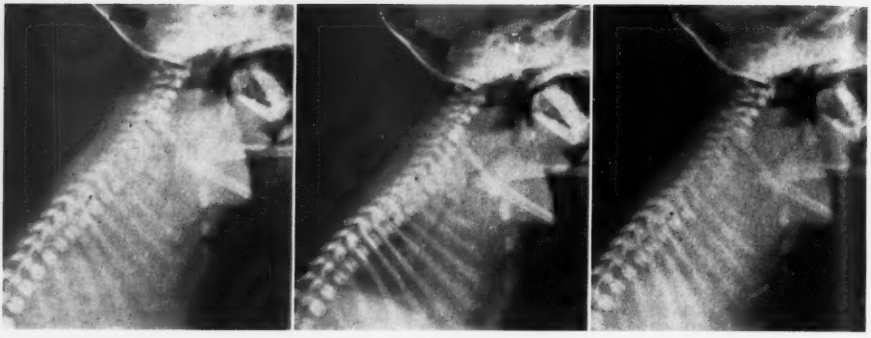

Fig. 9. Initiation of breathing with small amounts of residual air in the lungs. Lateral view, 3 pictures/sec. *a*) The thoracic cage is opaque. There might be small amounts of air in the lower posterior parts of the lungs. Note the dilated pharynx. *b*) Good air filling in the lung base. The trachea and the main bronchi are clearly delineated. Increased depth of the thorax. *c*) In the following expiration, there is again only traces of air to be seen in the lungs.

a very complete deaeration of the lungs during expiration (Fig. 9).

With the first air filling of the lungs, the cardiac outlines become delineated. In cases in which the cardio-thoracic ratio was measurable, no important variation in these measurements was discovered during the first 15 seconds after birth in cases were the umbilical cord was not clamped. If, however, the umbilical cord is clamped before the first breath, it is accompanied by a striking, step-wise diminution of the heart size during the first 3–4 cycles, followed by a corresponding cyclic increase in size. Apparently this transient decrease in heart size can be explained by the opening of the pulmonary vascular bed at the same time as the venous return through the umbilical vein is strangled. If the cord is not clamped, the loss of blood to the lungs is simultaneously replaced by blood from the placenta. The baby transfers the blood from the placenta to the lungs which have to take over the gas exchange.

To try to increase our knowledge of how the aeration of the lungs is established, Karlberg and co-workers (11, 15, 16, 17, 18) have made some studies of the lung ventilation and the mechanics of the first breaths during the first half minute of extrauterine life, at the age of 2–3 min, ½ hr, 1–2 hr, 1 day, and 1 week. Recordings of the first breaths showed various types of onset of breathing; from very regular ones to slow and irregular ones.

Independent of the start, all clinically visualized first breaths began with a negative intra-thoracic pressure determined by recording intraoesophageal pressure changes, which agree with the X-ray findings. In the first three breaths the inspiratory tidal volume range was between 20–75 ml, and the pressure required varied between 10–70 cm H_2O (values which were higher than previously expected). The pulmonary ventilation during the first 20 sec., timed from the beginning of the first breath, was found to be up to three times as large as in resting newborn in-

fants a few days old. It is evident that the pulmonary ventilation in normal alert infants is great immediately after birth.

With regard to the lung volume, there cannot be any residual gas in the lungs before the delivery. In some newborn infants, Karlberg and coworkers recorded a residual volume of 30–50 ml after the first breath, constituting about $\frac{1}{3}$–$\frac{1}{2}$ of the functional residual capacity (i.e. the aeration of the lungs at the end of a normal breath) at an age of 1–2 days. In some other newborns, the residual volume after the first breath was much smaller or not recordable at all. Using a closed circuit helium method, Karlberg and coworkers were able to show that the functional residual capacity continues to increase from the age of $\frac{1}{2}$–1 hr to $\frac{1}{2}$–1 day of life, but then remains fairly constant during the first week of life.

The longitudinal studies of the mechanic of breathing also indicate that the most rapid changes occur during the first few breaths and the following minutes. The compliance increases and the resistance of the airways decreases; therefore it follows that the respiratory work decreases rapidly.

These studies show that in healthy newborn infants the lung function is developed very rapidly during the first minutes of life and then considerably more slowly. After the child has reached the age of 1–2 days, the lung function seems to develop mainly along with the general growth and development of the child.

Before and during the first breaths, however, there is evidence that several factors may have an influence on the development of an adequate lung function, all of which cannot be discussed here. One of these is the adaptation of the foetal circulation to extrauterine life.

Tying the cord

When the umbilical cord is tied in the newborn lamb, Dawes noticed a rise in arterial blood pressure amounting to 5–50 per cent, with a mean of 19 per cent. After a variable interval of some minutes, the lambs become partly asphyxiated. The lamb makes respiratory efforts and, provided the airways are clear, the lungs are expanded for the first time (8).

Woodbury *et al.* (25) failed to detect any such rise in newborn infants following birth, although they were using the direct method with continuous recording. We have also been taking direct measurements in the umbilical arteries immediately after birth, and have not been able to see any significant rise (21).

Ashworth and Neligan (2) have worked out a sphygmomanometric technique especially for the purpose of permitting accurate and frequent recordings of the blood pressure and the pulse rate. According to their observations, clamping the cord has apparently no immediate significant effect on the systemic pressure.

Closure of the foramen ovale

Functional closure of the foramen ovale occurs almost immediately after birth. Barcroft (4) showed that the blood in the carotid arteries is 100 per cent oxygenated four minutes after ligation of the umbilical cord. In the newborn lamb, Dawes and his co-workers (10) found that with the onset of respiration the pressure in the

Fig. 10. Wide open foramen ovale in a newborn infant 18 hours old. Left anterior oblique projection. The stream of contrast loaded blood is divided into two streams of about equal size filling the right and the left atria.

Fig. 11. Closure of the foramen ovale in a newborn infant 7 days old. Left anterior oblique projection. Contrast injection into a malleolar vein. The child began to cry during the contrast injection. In one picture in the beginning of the angiocardiogram a small right to left shunt was seen at the atrial level. Now the shunt occurs at a higher level between the right and the left atria, indicating that the foramen ovale is almost closed and the patency is restricted to the upper part of the foramen ovale.

left atrium rises, due to a great and sudden increase in the pulmonary blood flow. When the circulation through the placenta is interrupted, there is a considerable fall of the inferior caval pressure. There are thus two principal reasons for the functional closure of the valves of the foramen ovale, a fall in inferior caval pressure, and a rise in the left atrial pressure. Our angiocardiographic observations on newborn infants indicate that this functional closure is not complete and readily reversible during the first days of life. Crying is sufficient to raise the right atrial pressure and to reopen the foramen ovale creating a big shunt (Fig. 10). In the second week of life, no shunts at rest and only small shunts during crying have been observed, indicating a progressive narrower slit between the valvula and the septum (Fig. 11).

Closure of the ductus arteriosus

Because of its muscularity and the special arrangements of the muscle bundles, the ductus arteriosus has been compared with a sphincter. In the foetus, the ductus is wide and the volume passing through it from the former to the latter is large. The question of the stimulus to normal ductus closure is a vexing one and

TABLE 1. *Data Obtained on Eight Normal Newborn Infants.*

Age hrs	Wght kilo	Heart vol. cc	Pressures R.V.	Pressures P.A. mm Hg	Pressures F.A.	Oxygen Content R.A.	Oxygen Content R.V. Volumes %	Oxygen Content P.A. Volumes %	Oxygen Content L.A.	Capacity
7	3.2	43	38/0	36/32	48	20.7	21.3	25.5	26.0	28.0
9	3.3	38	36/0	36/10	55	14.7	18.0	21.8	21.8	22.0
14	3.9	48	48/–2	36/18	47	13.9	16.7	20.0	22.0	22.0
18	4.5	40	50/0	50/10	—	19.7	20.3	21.3	—	—
75	2.3	20	20/8	16/0	—	18.6	19.6	20.0	—	24.3
76	4.3	58	40/–10	42/34	—	19.7	17.2	27.1	—	28.2
77	3.1	33	24/4	—	—	20.4	21.2	—	—	24.4
14d.	2.7	35	24/0	22/10	—	19.2	17.6	17.8	21.7	22.9

by no means certain. In recent years, attention has been focused on the role played by the oxygenation of the blood in the closure of the ductus arteriosus. Kennedy and Clark (19) showed that the closure of the ductus in the guinea pig could be effected by inspired oxygen, independent of any nerve supply to the ductus. Born *et al.* (5), using newborn lambs, noted ductus constriction in response to inflation of the lungs with oxygen. There was no constriction in response to inflation with nitrogen. The effect was seen even after sympathectomy and destruction of the brain and spinal cord, implying a direct effect of O_2 on the ductus. They also noted that in addition to O_2 as a stimulus to constriction, extreme asphyxia presumably via the release of sympathetic amines causes the ductus to constrict.

The timing of the closure has been the subject of much controversy. Until recently, it has been supposed that functional closure of the ductus occurred shortly after birth. Recent studies suggest that the ductus does, in fact, remain at least partially open for some time after birth. Using newborn infants without any signs of circulatory or respiratory distress, Adams and Lind (1) were able to find, on the basis of O_2 saturation studies at catheterization, the presence of left to right shunts at the ductus level even after the third day of life (Table I).

Another finding of interest was the presence of right ventricular and pulmonary hypertension of moderate degree. In addition, they demonstrated that the pressure adjustments within the heart after birth take place over a period of several days and not several minutes, as was previously supposed (Table I). If the Fick principle were to be applied and the oxygen consumption determined, the cardiac output in the newborn infant can be calculated. Three such determinations were made (Table 2).

Knowing the pressure relationships in the first three days of life, it seems quite likely that any procedure which might disturb the infant enough to increase the pressure in the pulmonary artery to more than the systemic pressure would produce right to left shunts through the ductus arteriosus. In a resting state, however,

TABLE 2. *Blood Flows Based on Actual Oxygen Consumption.*

Patient	Sex	Age	Weight grams	Lenght cms.	O_2 Consumption cc/min	Systemic blood flow cc/min	cc/min/kilo	Pulmonary blood flow cc/min	Shunt cc/min
G.B.[1]	F	9 hrs	2650	45	19.5	286	107	325	39
G.O.	F	6 days	3090	49	17.5	547	170	547	—
B.L.	M	7 days	3465	53	20.5	277	79	336	59

[1] This patient had a P.A. pressure of 40/30 and the systemic was 39 by the flush technique.

Fig. 12. Patent ductus arteriosus with right to left shunt. Newborn infant with a clinically inversed ductus syndrome. Left anterior oblique projection. Contrast injection into the right antecubital vein. The right side of the heart and the pulmonary artery are well contrast filled. The descending aorta is clearly seen. No contrast medium in the left side of the heart wherefore the descending aorta must be contrast filled through a patent ductus arteriosus.

the shunt is in the opposite direction: from the aorta to the pulmonary artery (Fig. 12).

Recently, in about one third of the newborn babies examined, Burnard (7) has succeeded in detecting and recording a faint cardiac murmur with certain characteristics, which are usually associated with flow through a patent ductus arteriosus.

Time does not permit me to dicuss more than a few aspects of the changes in the foetal circulation and lungs at birth. I have thus not mentioned the foetal circulation through the liver and the changes it undergoes at birth. This is because of limitation of time and certainly does not imply that these changes are not important and profound.

Summary

In any consideration of the neonatal adaptation to extrauterine life, it is not possible to separate respiratory from circulatory function, as the two are intimately cornected and mutually interdependent. In the foetus the lungs are not aerated, the pulmonary resistance is high, and the pulmonary blood flow reduced. Thus, the ductus arteriosus acts as a bypass for the blood around the "sleeping" lungs. Oxygenation and CO_2 exchange are carried out by the placenta. The comparatively well oxygenated blood, coming

from the placenta via the umbilical vein, reaches the inferior vena cava directly through the ductus venosus, which acts as a short circuit, and through the hepatic veins. From the inferior vena cava the blood is, for the most part, shunted through the foramen ovale into the left atrium, the left ventricle, and the ascending aorta, and is, to a significant extent, directed to the brain. The blood returning from the foetal head via the superior vena cava to the right side of the heart enters the right atrium and the right ventricle. It then passes, mainly via the ductus arteriosus, to the descending aorta to reach the placenta.

At birth, the lungs are aerated, the major factor in the lung expansion being the active inflation under negative pressure. If there is a strong successful inspiratory effort, there is a sudden and almost complete aeration of the lungs. This event acts as a focal point around which many of the changes in the circulation occur. The resistance in the pulmonary circuit drops, the pressure in the pulmonary artery falls, and the pulmonary flow increases. The increased pulmonary venous return increases the left atrial pressure which then exceeds that of the right atrium, and the valve of the foramen ovale closes more or less completely. These are rapid changes, normally occurring within a few minutes of birth.

The neonatal circulation thus established is characterized by a right ventricular and pulmonary arterial hypertension of moderate degree, a patent ductus arteriosus with a left to right shunt at rest, and a functionally closed foramen ovale, which is ready to reopen in response to pressure changes between the atria. The neonatal circulation, in turn, adjusts itself gradually over a period of several days. The pulmonary arterial pressure falls and, with the closure of the ductus arteriosus, the adult type of circulation is established.

The normal lung function seems, after the first breath, to get a "kicking" start during the first seconds or minutes of life, and then adjusts itself to the environment during the first hours of life. When the child is 1–2 days old, the lung function develops with the general growth and development of the child.

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ROENTGENOLOGIC STUDIES OF RESPIRATION IN INFANTS

By

JAMES F. BOSMA, J. FAWCITT, J. LIND,
YASUAKI TAKAGI and C. WEGELIUS

Almqvist & Wiksells Boktryckeri AB · Uppsala

UNIVERSITY OF MICHIGAN

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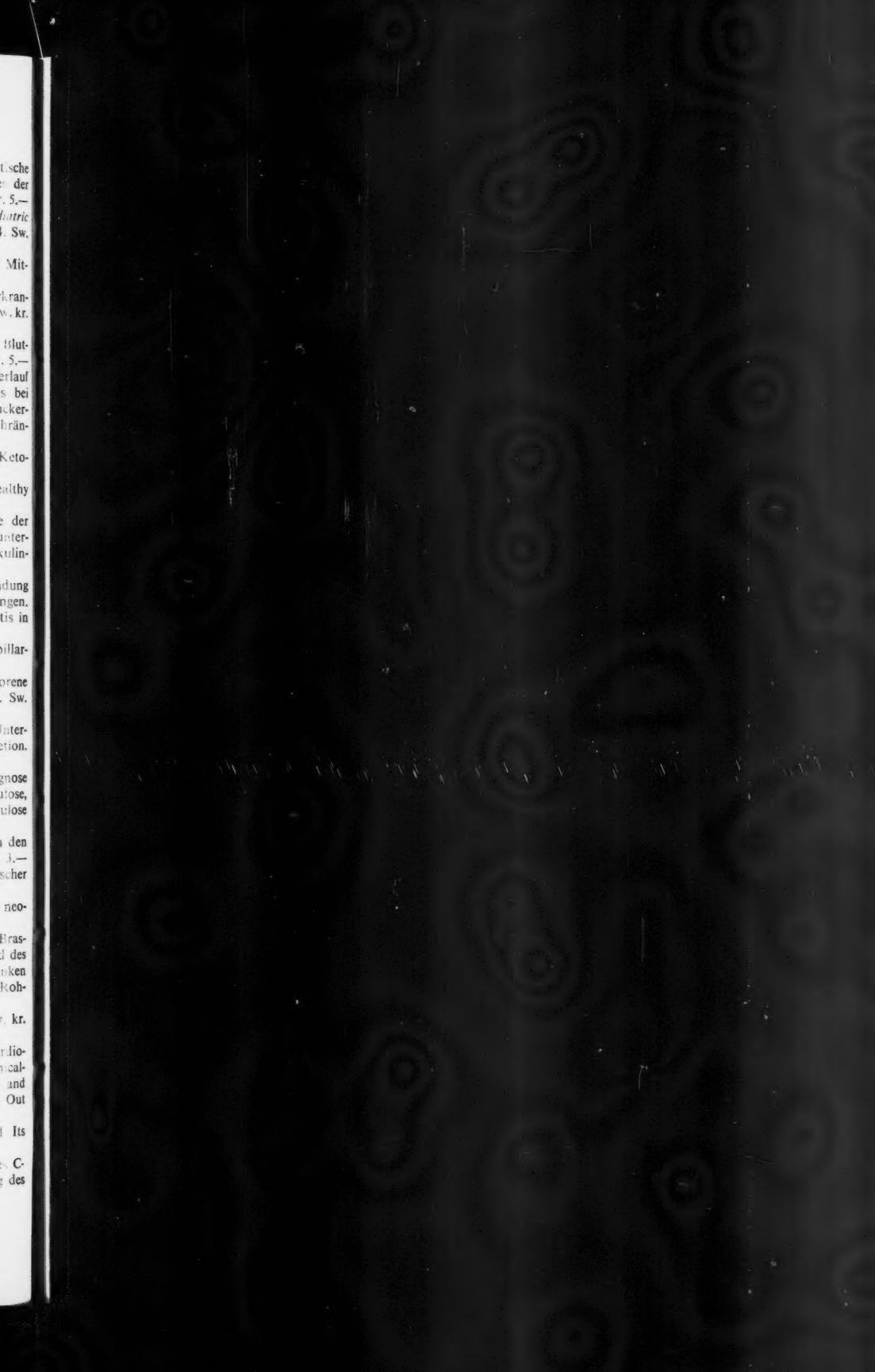

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ROENTGENOLOGIC STUDIES OF RESPIRATION IN INFANTS

By

J. F. BOSMA, J. FAWCITT, J. LIND,
Y. TAKAGI and C. WEGELIUS

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The First Breath

A Preliminary Communication Describing Some Methods of Investigation of the First Breath of a Baby and the Results Obtained from Them

by J. FAWCITT, J. LIND and C. WEGELIUS

The most important action in any person's life is the first breath, when the transition from the oxygenation of the foetal tissues by the maternal circulation to oxygenation of the blood by the baby's own respiratory efforts takes place. This may occur as the head emerges from the birth passages or may be delayed for many seconds after delivery.

It has been found possible by rapid serial roentgenography to study pictorially the details of the initial respiratory efforts in the newborn infant and to show the pattern of the primary aeration of its lungs.

Since the drop in the mortality rate of infants in their first hour or two of extrauterine existence has not kept step with that of the slightly later age groups, it has been considered that any method which would lead to the greater understanding of neonatal respiratory physiology would be of value.

Method

High speed roentgenographic techniques are essential in the analysis of alterations in the shape of the thoracic cage and of the rapid aeration of the lung fields after birth. These roentgenological examinations cannot be limited to the extremes of the full inspiratory and expiratory phases but must include an adequate number of films of intermediate stages, so that the dynamics of the complex processes of the first and subsequent breaths may be adequately recorded. A Schönander AOT Film Changer capable of 6 exposures per second was used, with serial films of 24 × 30 cm size. The X-ray equipment was placed at the foot of the labour bed with the mother in the supine position with her perineum at the end of the bed so that the infant was delivered direct onto the flat surface of the serial device.

Direct full size roentgenography is preferable to cineradiography for the interpretation of the details of the anatomical structure because of the greater size of the films and correspondingly increased detail shown in them.

Two special technical difficulties in obtaining roentgen recordings of the first breath should be mentioned here.

The instant of commencement of respiration was unpredictable, and in some cases it was not possible to get the infant into position, and relatively motionless on the casette before breathing commenced. As breathing usually started with great promptitude the exposures had to be begun as soon as possible after delivery, but if, on the other hand, the infant was slow to breathe, the series of roentgenograms or the roll of film might be finished before respiration commenced.

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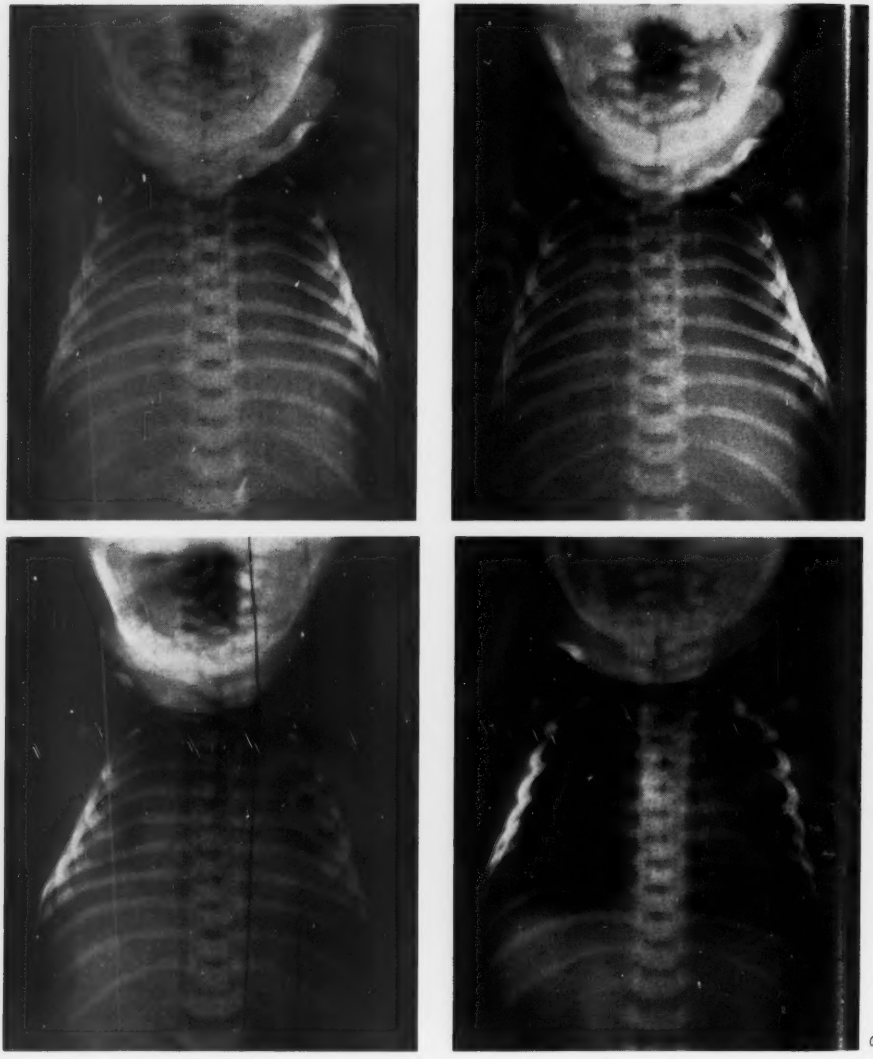

Fig. 1. Male infant: 3650 g birth weight. Films taken at a rate of 2/sec. AP projection. Normal delivery. During the first 9½ seconds there was no evidence of respiratory effort. *a*) At the 20th film (10 sec.) some air was visible in the mouth. *b*) The 21st film shows increased air in the mouth but no real significant aeration of the lungs. *c*) The 23rd film demonstrated still more air in the mouth, with slight filling of one or two of the major bronchi and very slight aeration of the lungs and the cardiac outline was hazily seen. There was marked diminution of the thoracic diameter due to the primary inspiratory effort. *d*) The next film (24) revealed very satisfactory aeration of both lungs with sharp delineation of the diaphragmatic and cardiac contours. The phase shown that of full inspiration. This was an example of really satisfactory inspiration leading to virtually complete aeration of the lungs. Rib insuction was not very dramatic in this case.

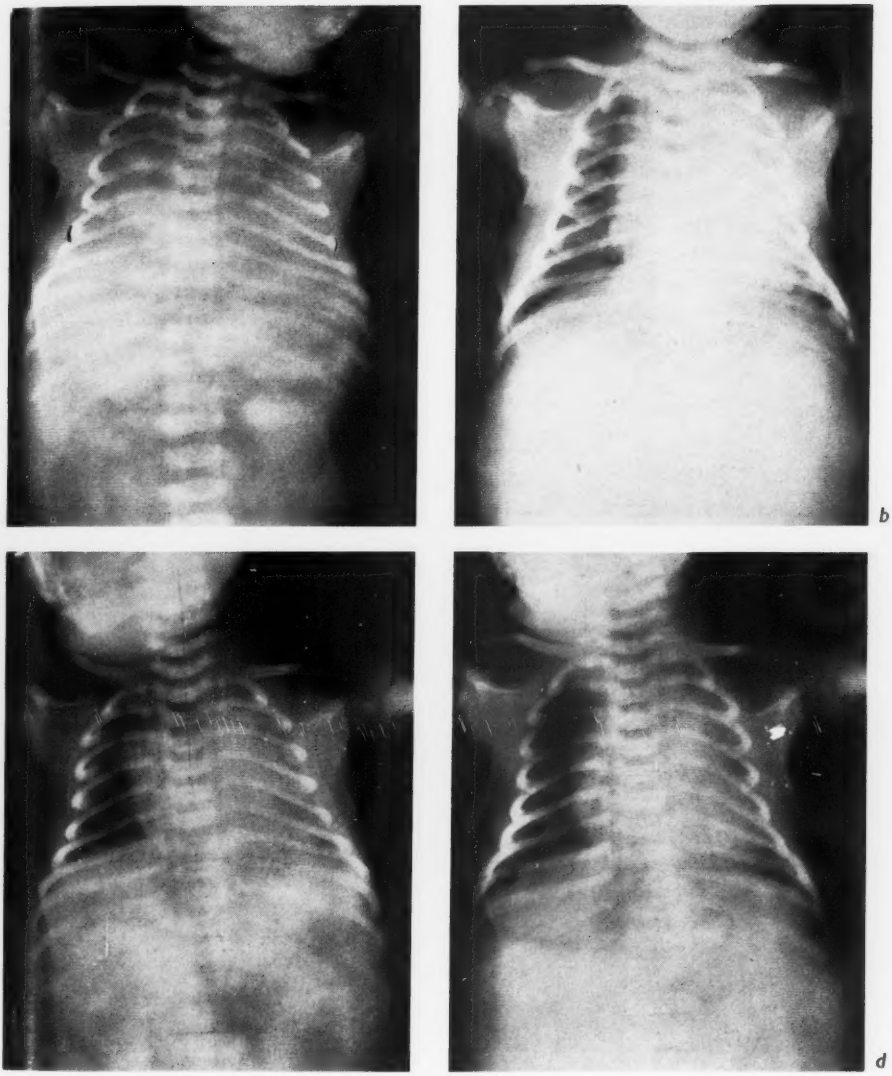

Fig. 2. Female infant: 4200 g birth weight. Films taken at 2/sec. in the AP projection. Normal delivery with no breath taken until 7½ seconds after delivery. *a*) A film taken at 7½ seconds showed no aeration of the lungs. *b*) At 8 seconds there was marked insuction of the thoracic cage at the level of the 5th and 6th ribs. A fair degree of aeration had taken place, though the left upper lobe was incompletely filled and the diaphragms were low. *c*) Five and a half seconds later, a futher breath commenced in the 27th film (13½ secs). There was a fair degree of aeration present with high diaphragms and a poorly aerated left lung. *d*) The 14 second film showed well marked insuction of the ribs; improved aeration of the lungs and low diaphragms. This series showed marked waisting of the thoracic cage and a low diaphragmatic level with the first breath, which was fairly satisfactory. A more complete aeration of the lungs was achieved with the second breath which also gave rise to some thoracic waisting.

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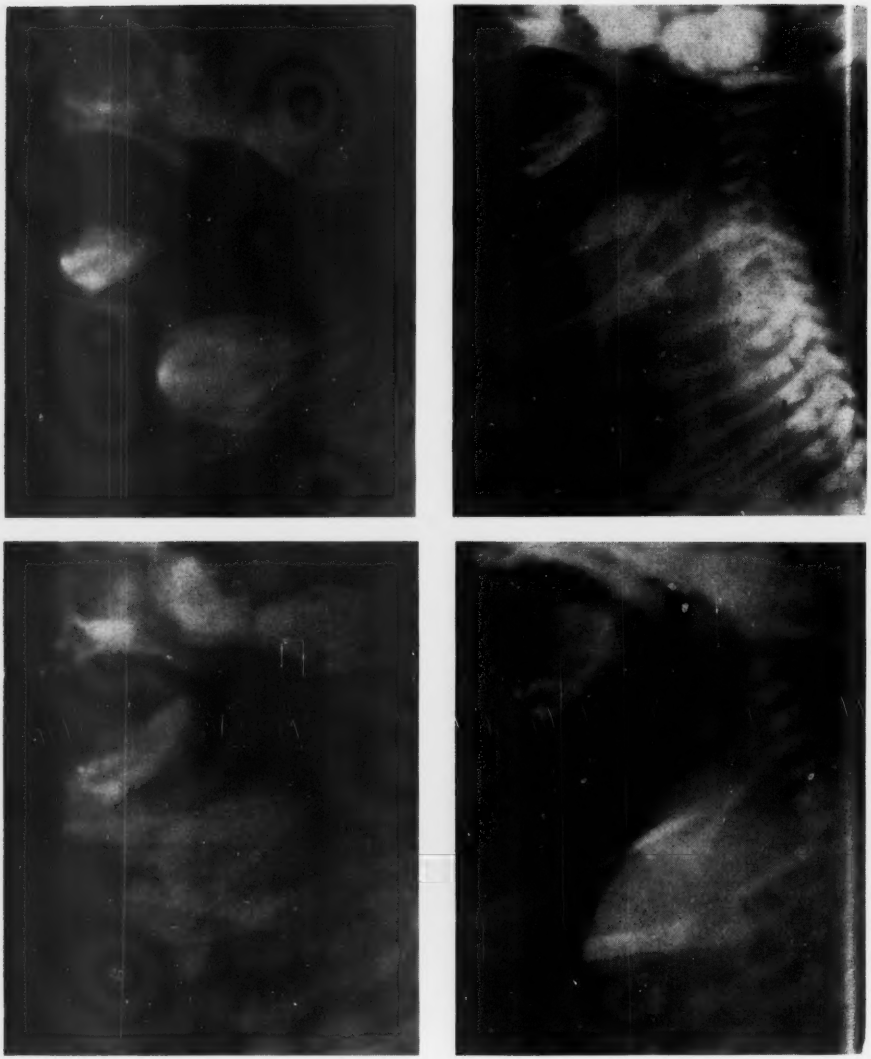

Fig. 3. Female infant: 3820 g birth weight. Films taken at 3/sec. in the lateral projection. Normal delivery with no breath taken before commencement of the radiographs. *a*) After 2 seconds some air was present in the mouth; and had reached as far as the larynx. The soft palate is outlined but there was no air in the trachea or lungs. *b*) The 8th film (2.6 secs) showed more air in the mouth, and pharynx and a neutral position of the tongue. *c*) At 3.3 secs (Film 10) there was much less air in the mouth and pharynx and the tongue was pressed against the palate. *d*) The 7 second film (24) showed air in the upper edge of the trachea, the tongue remaining in the neutral position.

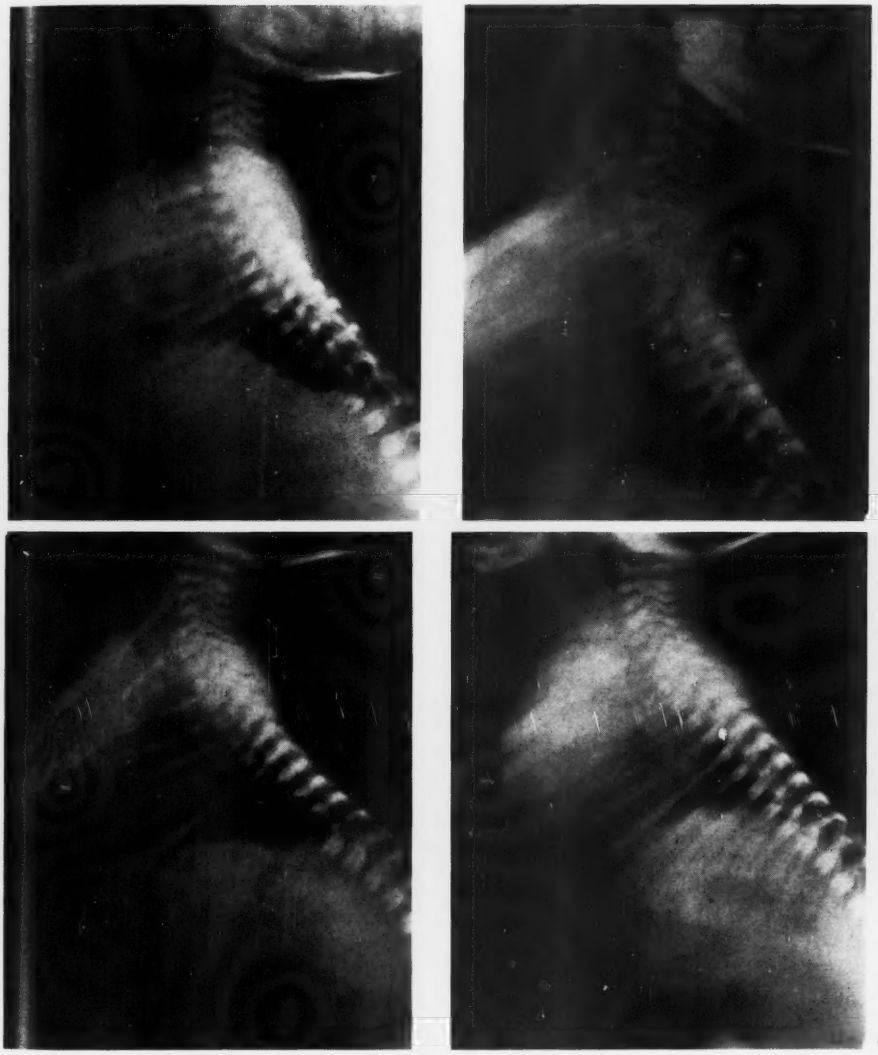

Fig. 4. (Case 3 continued) *a*) The 25th film (8.3 secs) showed the trachea outlined for the first time with aeration of the lungs wich was at yet very incomplete. There was a great bolus of air in the pharynx. The sternum had moved upwards as well as outwards. *b*) The 26th film (8.6 secs) showed dilatation of the trachea. There was better aeration of the lungs. The amount of air in the pharynx was reduced. *c*) No. 27 (9 secs) showed commencing deaeration of the lungs and some reduction in the tracheal calibre from the previous film. There was some kinking of the trachea in the upper thoracic and cervical regions. *d*) No. 29 (9.6 secs) showed very little air in the trachea and very marked deaeration of the lungs. There was even less air in the pharynx than in the previous illustration. This case showed the halting of the air in the pharynx, its gradual tippling through the larynx and rapid, indeed almost instantaneous progress down the trachea into the bronchi and alveoli. Reasonable aeration of the lungs occurred in this first breath. The variation in the tracheal calibre was a notable feature as was the upward lifting of the sternum on inspiration.

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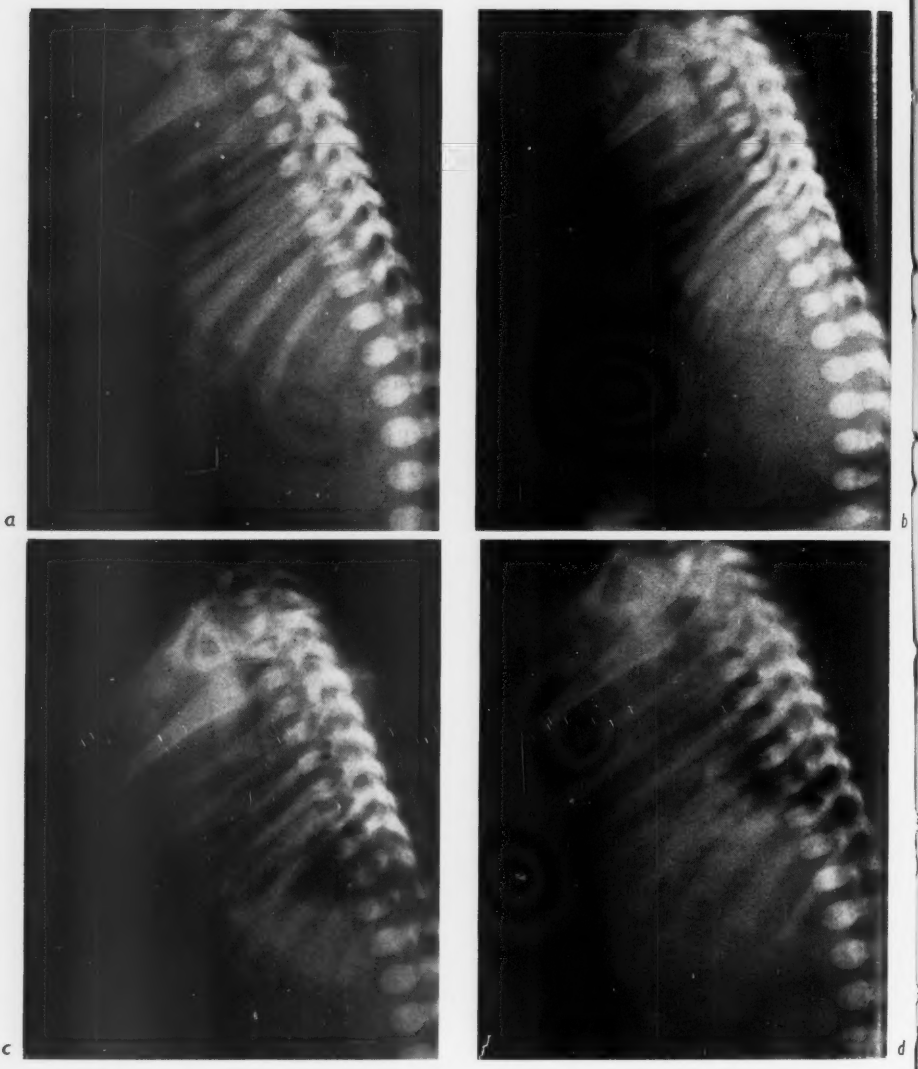
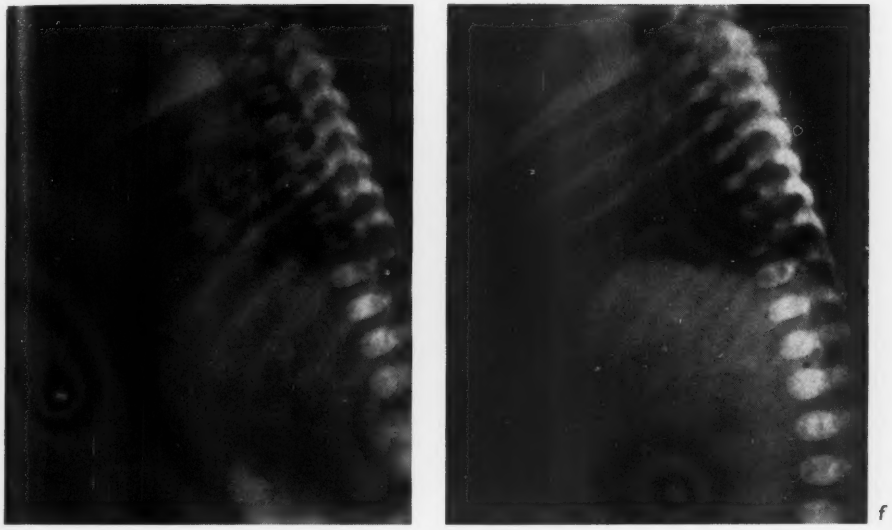


Fig. 5. Male infant: 3180 g birth weight. Films taken 2/sec. in the lateral projection. Normal deliver . *a*) There was no evidence of air in trachea or thorax in Film No. 2. *b*) The 6th film (3 secs) reveale l the tracheal outline and that of the left main stem bronchus. The thoracic depth dipped sharply fro a 48 to 44 mm between the 5th and 6th films. *c*) The next film (3½ secs) showed rather poor aeration f bases of the lung fields posteriorly. The diaphragms were hazy and the cardiac shadow virtuall not distinguishable. *d*) At 5½ seconds aeration remained poor and the tracheal calibre rather narro with slight anterior bowing in the lower portion of the neck. *e*) At 9 seconds stil lmarked deaeratic and a trachea narrowed. *f*) At 10½ seconds there had been markedly improved aeration with sharpl



outlined diaphragms. The posterior portions of the basis were very much better aerated than the rest of the lungs. These films demonstrated the initial aeration of the trachea and main stem bronchi without illumination of the lung, followed within half a second by rather poor pneumatisation of the lungs in this first breath.

Despite these inherent problems the majority of the roentgenological investigations showed points of value.

X-ray Dosage

The possibility of excessive radiation of the infant was carefully considered and certain safeguards were employed. The examinations were carried out with careful coning of the primary beam; as far as possible the infant's gonads were shielded with lead rubber, corresponding to 2 mm of lead.

Measurements carried out during the procedure by the Radiophysics Institute gave the following skin doses.

4OT Film Changer. Fifteen exposures—50 mrmr—total dose 0.6 "r" units. Exposure factors: 70–78 kV–200 mA—0.02 sec.

These values indicated that the irradiation appeared to be harmless especially if the careful coning was taken into account.

Subjects

The infants under study in this project were normal newborn infants born at term of normal pregnancy and delivery accomplished with minimal maternal sedation. The umbilical cord was not clamped before the radiographic examination.

Case Analysis

The Schönander films of each case were analysed individually. In addition to the description of their distinctive features, measurements were made of the changes in thoracic width in the AP films and the thoracic depth in the lateral films. When the diaphragm became visible after the first respiration, its mean level was reported. (A fully investigated case is shown in Appendix 1.)

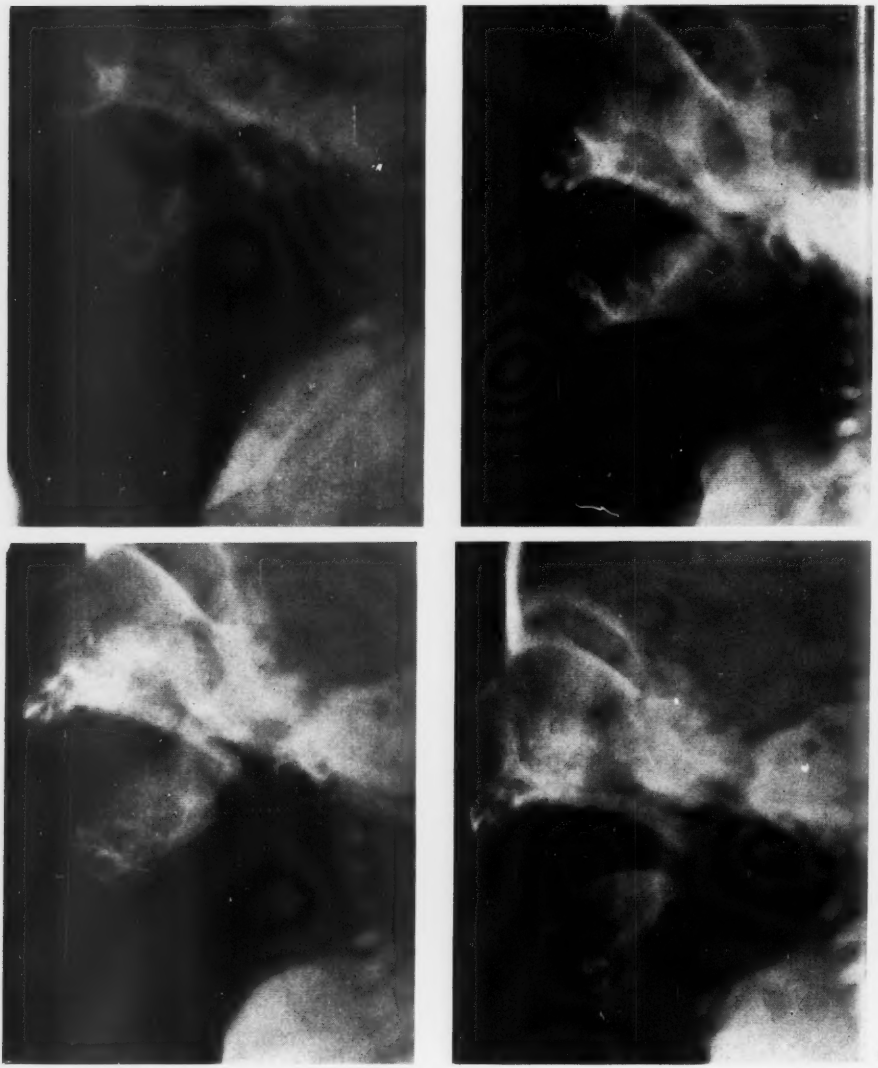


Fig. 6. Female infant: 3500 g birth weight. Films taken at 2/sec. lateral projection. Normal delivery. Localised views of the upper respiratory passages are illustrated in this series. *a*) In the 13th film no aeration had occurred but air was seen in the pharynx and tipping towards the larynx. The tongue is placed forwards. *b*) At 7½ seconds—the tongue had swept backwards, in apposition with the soft palate and air is seen in the dilated trachea. There was good aeration of the lungs. *c*) The next film showed marked deaeration of the lungs, a dilated pharyngeal area and a narrowed trachea. The tongue seemed to be commencing a forward movement. *d*) Half a second later (8½ secs) the tongue had been pushed forward by the expiration and the pharynx was empty of air. The full sized film showed deaeration of the lungs. This case demonstrated some of the movements of the tongue and pharynx prior to the first inspiration and showed their position during expiration.

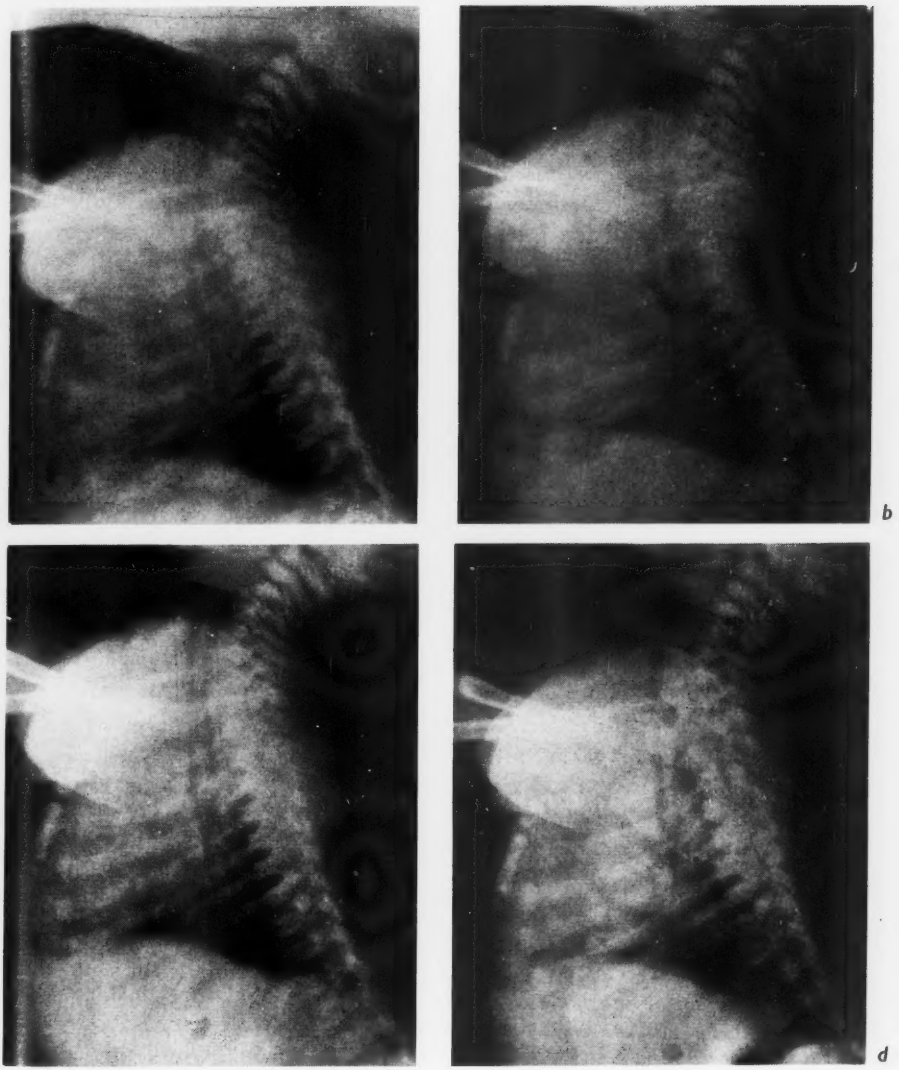


Fig. 7. Female infant—a satisfactory breath before the commencement of the roentgenological investigation at 2 films per second. Air was noted in the oesophagus by ten seconds already. *a*) In the 25th film (12½ secs) the upper oesophagus is clearly seen behind a trachea which is well filled with air. *b*) The next film shows relatively little air in the upper oesophagus and a bolus of air just above the diaphragm. No air was seen in the stomach at this stage. *c*) A film taken at 14½ seconds reveals the majority of the upper two thirds of the oesophagus filled with air and a fleck of air in the stomach. *d*) At 15 seconds oesophagus is almost empty of air and the spot of air present in the stomach. This series demonstrates the first air in the stomach and the clear visualisation of the oesophagus. This was the only occasion in which the stomach bubble was shown in the first fifteen seconds of extra uterine existence.

Discussion

The complete histological picture of the infants' lungs just before birth is still not well known. Most experts, however, seem to agree that the lungs, at that stage, show a pattern of well developed ducts. The alveoli are not quite distended, nor entirely collapsed but present the picture of a crumpled sac.

At birth, after the head of the child is delivered, the thoracic cage is compressed during its passage through the birth canal. As a result of this compression, mucus and amniotic liquid is squeezed out through the nose and the mouth of the child. As soon as the thoracic cage is delivered it gets back its former shape, due to its elasticity. This recoil might also be promoted by the compression of the abdomen which pushes the diaphragm upwards. By this elastic recoil the amniotic fluid expressed is replaced by air. This is a passive mechanism of filling of the respiratory passages with air.

During the very short period between delivery and the onset of respiration, there is complete radio-opacity of the thoracic cage with the heart and diaphragmatic outlines not defined. The rib configuration does not suggest "collapsed" lungs but has an almost horizontal course (figs. 1a and 8). Air is seen in some cases in the upper airways, lipping into the trachea or even into the main bronchi occasionally.

Rapid sequential radiographs which demonstrate the pharyngeal and cervical area, as well as the trunk, show that both the upper and the lower motor mechanisms are involved in initial air inflation of the lungs (1, 2). This inflation occurs against a background of organized performances in the pharyngeal area. In the serial lateral radiographs the successively increasing air filling of the pharynx and larynx appears to be an active process, filling the airways before the first breath.

Prior to air inflation of the lung, there is almost invariably a fair degree of insuction of the thoracic cage which is most noticeable at the level of the 4th, 5th and 6th ribs in the A–P view. This insuction may occur repeatedly before the first inspiration. The degree of rib insuction may vary considerably, that of the greatest degree usually accompanying the first aeration of the lungs.

The thoracic cage expands with the first inspiration, primarily due to a contraction of the diaphragm. The air first fills the lower part of the thorax which, to begin with, is the only expanding part of the cage, the lateral walls showing varying degree of insuction, due to the strong pulling of the diaphragm.

a) If there is a strong successful inspiratory effort the trachea is dilated and there is complete or almost complete radiological aeration of both lungs. The cardiac and diaphragmatic outlines become sharply delineated. If this first good inspiratory effort is markedly successful the diaphragms appear low in position.

b) If there is a relatively poor inspiratory effort, the trachea does not dilate up to quite the same degree as in a good primary breath and the amount of aeration may be much more incomplete. It is now clearly seen that the posterior portion of the bases of the lungs aerate earlier and more completely than the upper and anterior parts of the lungs. The cardiac and diaphragmatic outlines tend to be hazy and ill defined in a poor initial breath.

One or more lobes of a lung may not aerate with the first breath.

Following the first inspiration there can be very gross deaeration of the lungs during expiration, with narrowing of the trachea to a thread of lumen. This degree of deaeration may take place even after a successful inspiration with good aeration of the lungs. As the trachea narrows it shows a slight forward bowing in the upper thoracic and lower cervical regions.

The cardiac and diaphragmatic outlines become almost indistinguishable against the background of deaerated lung tissue. Where the diaphragms are visible they are at a higher level than during the phase of inspiration.

This phase of deaeration lasts for several seconds until the commencement of the next breath.

Later respirations do not normally give the same degree of rib insuction as the initial breath, but if there has been poor aeration of the lungs to begin with, there is at any rate, some "waisting" of the thoracic cage at the initiation of the second breath.

The trachea normally becomes dilated again during the period of inspiration: the lungs are much more aerated and there is downward movement of the diaphragms.

But the diaphragm and the cardiac outlines become very much more sharply delineated.

During the first breaths a variable degree of pharynx-larynx closure may be seen, a mechanism which might prevent an egress of air from the lungs and may, during the phase of high positive pressure, facilitate further distribution of air within the lungs (1, 2).

Whilst the oesophagus was seen as an air filled passage separate from the trachea in several of our cases, and a bolus of air was seen above the diaphragm, it was only in one case that a tiny amount of air was seen in the stomach 14 seconds after the commencement of the exposure.

An attempt was made to correlate variations in the cardiac size during the examinations, but in cases in which the cardio-thoracic ratio could be measured, no important variation in this measurement was discovered in the first 15 seconds after birth. Some of the stages of the initiation of respiration which have been described tend to merge into each other to a considerable degree and there is wide variation in the roentgenological picture.

Summary

The roentgenological appearances of the thoracic cage and the lungs in the first breath of the infant, which has been undertaken with high speed technique, have been described, and a number of the patterns produced have been assessed.

The inherent difficulty of the commencement of respiration in the foetus has been underlined by the insuction of the thoracic cage in the majority of the cases. The alteration in the calibre of the trachea is a notable feature.

The extraordinarily rapid and complete aeration of the lungs is particularly noteworthy.

Appendix 1 28.6.57

Case I

Female infant. Weight 4200 g. Length 63 cm.
Mother para 5. 1st Stage 6 hrs. 2nd Stage 8 mins. Normal delivery.
No cry or breath before films. Vigorous breathing after films began.
Roentgenological features.
Technical features 78 kV. 200 ma. 0.02 sec. 2/sec. AP.

	Thoracic breadth	Diaph. level	
1.			? slightly post mature (humeral epiphyses).
2.	89 mm	—	Slight waisting of thoracic cage—? at level of diaphragm with abdominal contents spreading lower ribs.
3.	89 mm	—	Similar
4.	89 mm	—	Similar
5.	89 mm	—	Similar
6.	89 mm	—	Similar
7.	89–90 mm	—	Slight loss of waisting—? rotation.
8.	93 mm	—	Similar
9.	90 mm	—	Similar
10.	89 mm	—	? slight increased waisting
11.	90 mm	—	Similar
12.	94 mm	—	Similar
13.	91 mm	—	Similar
14.	93 mm	—	Similar
15.	93 mm	—	Similar
16.	*84 mm*	8½–9½	The first hint of aeration with marked insuction of ribs and good aeration of right lung in complete aeration LUL but L. base shows aeration.
17.	93 mm	7½–8	Aeration now evident LUL but somewhat incomplete.
18.	93 mm	6½–7	Diaphragms slightly raised, slight deaeration has taken place.
19.	93 mm	6½–7	Position of diaphragms and degree of aeration unchanged within minor limits.
20.	92 mm	6½–7	Degree of aeration unchanged.
21.	93 mm	7–7	Degree of aeration not materially changed.
22.	92 mm	6½–7	Degree of aeration materially changed.
23.	93 mm	6½–7	Degree of aeration not materially changed.
24.	93 mm	6–6½	Possibly slight degree of deaeration taking place.
25.	92½ mm	6½–6½	No gross material change. Degree of aeration I.S.Q.
26.	94 mm	6½–7	No gross change.
27.	94 mm	6½–7	There is perhaps a minor degree of deaeration taking place.
28.	88 mm	8½–8½	There is some rib insuction and improved aeration of the lung fields The basal bronchial outlines are well seen (inspiratory phase).
29.	95 mm	7½–8	Improved aeration L. heart outline well seen. Full inspiration.
30.	95 mm	7–7½	Slight deaeration—diaphragms rising (expiratory phase).

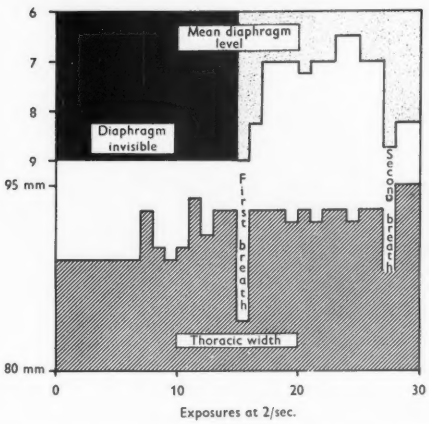


Fig. 8. Graphic representation of the changes in thoracic width and mean diaphragm level caused by the first 2 breaths in life (Appendix 1).

Acknowledgements

We wish to acknowledge with thanks the co-operation of the Director and Staff of the Southern Maternity Hospital, Stockholm, and assistance of Miss Jean Perry, Medical Illustrator, Crumpsall Hospital, Manchester.

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Roentgenologic Observations of Motions of the Upper Airway Associated with Establishment of Respiration in the Newborn Infant

by JAMES F. BOSMA[1] and JOHN LIND[2]

These studies were performed at the Southern Maternity Hospital, Stockholm, under sponsorship of the Wenner-Gren Cardiovascular Research Laboratory and the Association for the Aid of Crippled Children. The costs of preparation of this material have been borne by the National Foundation, the United States Public Health Service, and the Wyeth Laboratories.

Introduction

Procedures of a continuing study of natal transition (1, 2) have been adapted to provide radiological demonstration of participation of the pharynx and larynx in the initiation of respiration. A preliminary report (3) has described an unusual action of swallowing air into the trachea ("glossopharyngeal respiration") in association with natal respiration. The present studies include a larger number of infants, in some of whom a more rapid radiographic method is employed.

It is apparent from these radiographic observations that the whole of the respiratory pathway is involved in establishment of respiration. In the majority of these newborn infants, the pharynx and larynx moved in recognizable performance patterns. These motions were distinguished into either of two principal patterns; one of which was a cephalo-caudad engulfing action resembling swallow, and the other a constriction action essentially similar to the usual postnatal motions of pharynx and larynx in modulations of respiration. The former pattern of motion was that of glossopharyngeal respiration (GPR) in paralysis-disabled poliomyelitis patients (4–7) or as a part of focal stem seizures in an infant (8). In the motions in this pattern observed in these newborns, there was commonly a coincident motion within the trunk, but this general combined performance of pharynx region and trunk is termed "glossopharyngeal" by reason of its similarity to this form of respiration in other clinical circumstances. The other general pattern of motion, similar to usual patterns of motion in respiration, was distinguished by comparative stability of the hyoid and laryngeal position. Pharyngeal occlusion or constriction was accomplished by motions of pharynx wall, tongue, and palate in relation to this stable base. This pattern of action is here termed "pharyngeal constriction".

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The variations observed include lesser degrees of action within either of these patterns of pharynx participation in natal respiration. There are also associated extension and flexion at neck, and opening or closing of the mouth in the manner of gasping, "*Schnappen*" (9). Motions of sucking are also seen incidental to initial filling of the pharynx with air. Swallows of air into esophagus are interspersed among the respiratory maneuvers, and in some infants precede gross pulmonary aeration. Grunt and cry are noted to be variants of the constriction pattern.

Subjects and Procedures of the Study

The infants under study in the project were born at term of normal pregnancy and of cephalic delivery accomplished with minimal chloroform maternal anaesthesia. The normality of these infants was further evidenced by their normal subsequent condition in the newborn period, as observed by one of these authors (J. L.).

The infants were delivered directly upon the Schönander roentgen table and held in position for lateral exposures, centered in the shoulder area. Placement of the infant in this position required approximately one to three seconds after completion of delivery. They were unmoved during the roentgen exposures and subsequently, until spontaneous cry was well established. In particular, no attempts were made to stimulate onset of respiration. The umbilical cords were not clamped.

In the later infants of this series, coincidental phonatory recordings were obtained from a large surface microphone held against the infant's thorax, and the limited oscillogram was recorded by an Elema ink-writing phono-cardiographic apparatus. The visual and acoustic observations were correlated in detail immediately upon completion of each study.

Details of the radiological procedure are described elsewhere.[1] Evaluation of individual films was by inspection, by tracings which might be overlaid for comparisons, and by caliper comparisons of selected points. By reason of the constancy of subject distance from film, relative measurements of displacement of parts could be made of successive films of each infant without attempted correction or interpolation of actual distances. All these displacements are reported in terms of direction or gross extent with no specific measurement of them.

The common criterion sites of the head and neck area were *mid-sella turcica*, *anterior nasal spine*, *upper incisor tooth*, *menton*, middle of the *hyoid body*, middle of *odontoid process*, and inferior aspect of the occipital bone. And in the trunk, the mid-point of the *lowest calcified sternal ossification center*, ventral margin of the *vertebral column*, cephalic margin of the *uppermost side of the diaphragm*, and the *iliac crest*. The superimpositions were aligned at the odontoid and the middle thoracic vertebrae, so that anteroposterior displacements of the spine were indicated in the lower cervical, the upper thoracic, or in the lumbar vertebrae. In some series, not illustrated here, in which much head motion occurred, comparison superimpositions were aligned at the odontoid and the occipital bone, so that the pharyngeal and oral motions could be described in relation to the head.

In these lateral radiographs, it was possible to discern changes in alignment of head, neck, and trunk, in opening or closing of the mouth, motions of the tongue, palate, dorsal pharyngeal wall, arytenoid masses, and vocal folds. Approximation of the arytenoid mass to the epiglottis could be discerned with adduction of the vocal cords, but partial adduction of the cords could not be distinguished from their complete closure. The motions of the diaphragm and the ventral wall of the thorax and abdomen were also apparent.

The motions of the hyoid bone epitomize the actions of the pharynx area, for extrinsic muscles supporting the pharynx converge upon the hyoid, and it also constitutes the principal attachment of the middle portion

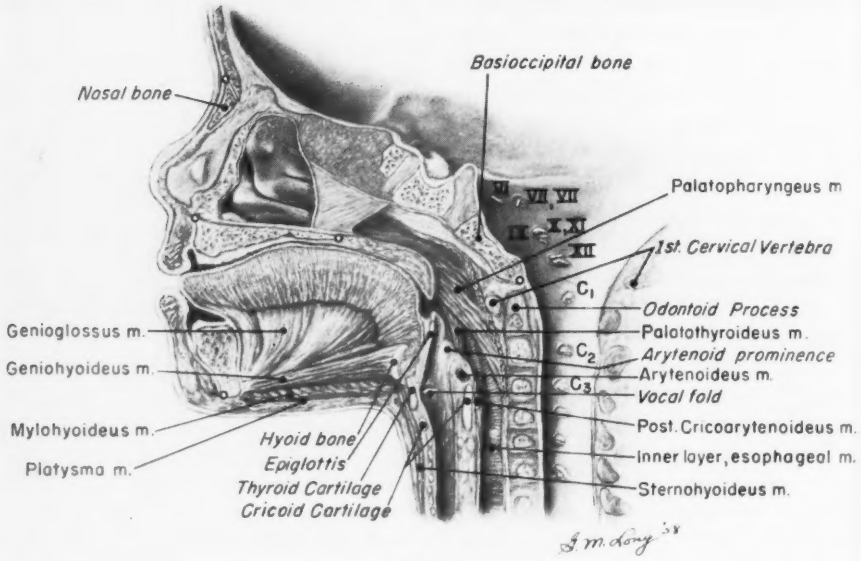


Fig. 1 *A*.

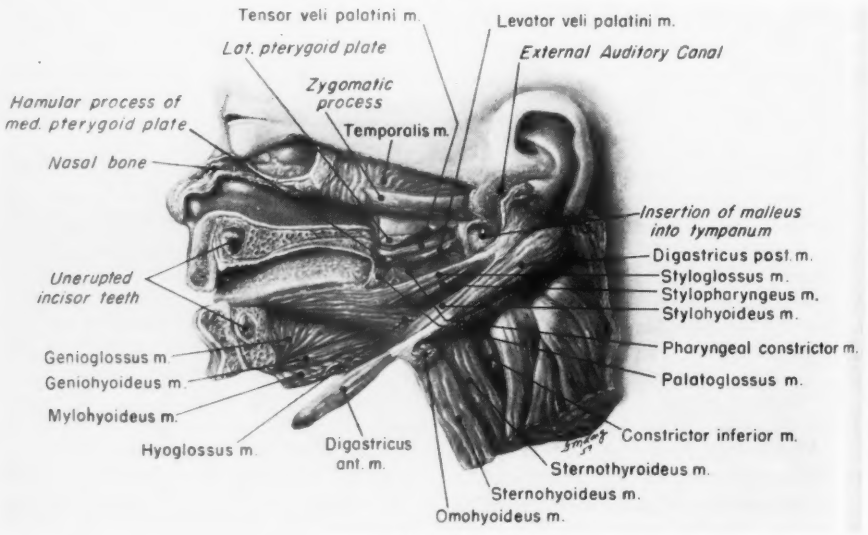


Fig. 1 *B*.

Fig. 1, *A* and *B*. Dissections illustrating the musculature of the pharyngeal region in the term newborn infant. *A*. Saggittal view of pharynx and mouth. Mucosa of the pharynx is removed and the larynx and trachea are displaced ventrad to show the intrinsic pharyngeal muscles. The cephalometric points of nasion, basion, anterior and posterior nasal spine, and menton are indicated by white dots.

B. Suspensory musculature of pharynx and tongue. Digastricus anterior and mylohyoideus muscles are deflected downward to facilitate demonstration of geniohyoideus and genioglossus muscles.

of the constrictor, the dorsal fulcrum of the tongue and the support of the larynx (Fig. 1 *A* and *B*). A particular advantage of its use as a criterion in these studies is the radiologic demonstration of the hyoid body, which is frequently calcified in the term newborn infant.

The position of the hyoid body was evaluated in relation to sella and to the odontoid process. The position of the most caudal ossified sternal center was determined in relation to the hyoid, odontoid, the ventral margin of the vertebrae, and the iliac crest. General motions of the head and neck were described in relevance to the lower thoracic spine. In this circumstance of vertical alignment of roentgen target and film, there were no distinguishable levels of interface of air and amniotic fluid. For further distinction of soft tissue details, critical films were subjected to electronic intensity amplification employing LogEtronic apparatus.[1] These films used in illustration of this report are so intensified.

It is recognized that these studies record achieved position at the moment of observation and that caution is required to interpret motions from the changes in position which they demonstrate. Despite this limitation of comparative infrequency of observation, it was possible to recognize these organized motions, particularly as multiple criteria were employed in their identification. Inferences of particular muscular actions were made with awareness of the complexity of motor interaction in the pharynx region. The reader is referred to the attached illustration of the muscular arrangements of this region (Figs. 1 *A* and 1 *B*). The sella, odontoid, hyoid body, and most caudal ossified center of the sternum are numbered on initial radiographs and tracings of each series. In the tracings of succeeding stages of progression or of change, the interrupted lines and hollow dots are of recent position and the solid lines and dots are of the current position illustrated. In these illustrations, the example radiographs are adjacent to tracings which are matched in projection, to facilitate plotting comparisons within each series. The directions of displacement are described in relation to the infant by the terms *cephalad*, *caudad*, *ventrad*, and *dorsad*.

[1] These amplifications were performed by the Hospital Picture Service, Red Bank, New Jersey.

Observations

Technically satisfactory radiographic series were obtained on 30 newborns. Thirty films were obtained on each subject at intervals of half-second in 13, third-second in 3, quarter-second in 1, and sixth-second in 13 infants.

A variety of sequences of particular performances of the upper respiratory way have been distinguished in this study. These proceed upon various schedules, with pauses of apparent absence of motion interspersed among them. These pauses of apparent inaction are actually sustained poses of static activity and not positions of passive immobility or "rest". The static motor activity governing the position of these pharynx region structures was indicated by their position or contour. Thus, at the time of pause prior to participation in specific action, the tongue tip was commonly raised (compare Figs. 3 and 4) and the anterior portion of the tongue might be in a cupped contour (as in Figs. 3 *H* and 4 *G*). The palate might be angled sharply dorsally in the portion into which the levator muscles are inserted (as in Figs. 4 *B* and 4 *G*), or the palatopharyngeal folds might stand out sharply. The laryngeal ventricle might be prominently demonstrated, indicative of activation of the musculature adducting the true and the false vocal cords, provided the transverse roentgenographic alignment was appropriate for this demonstration (compare Fig. 4 *B*).

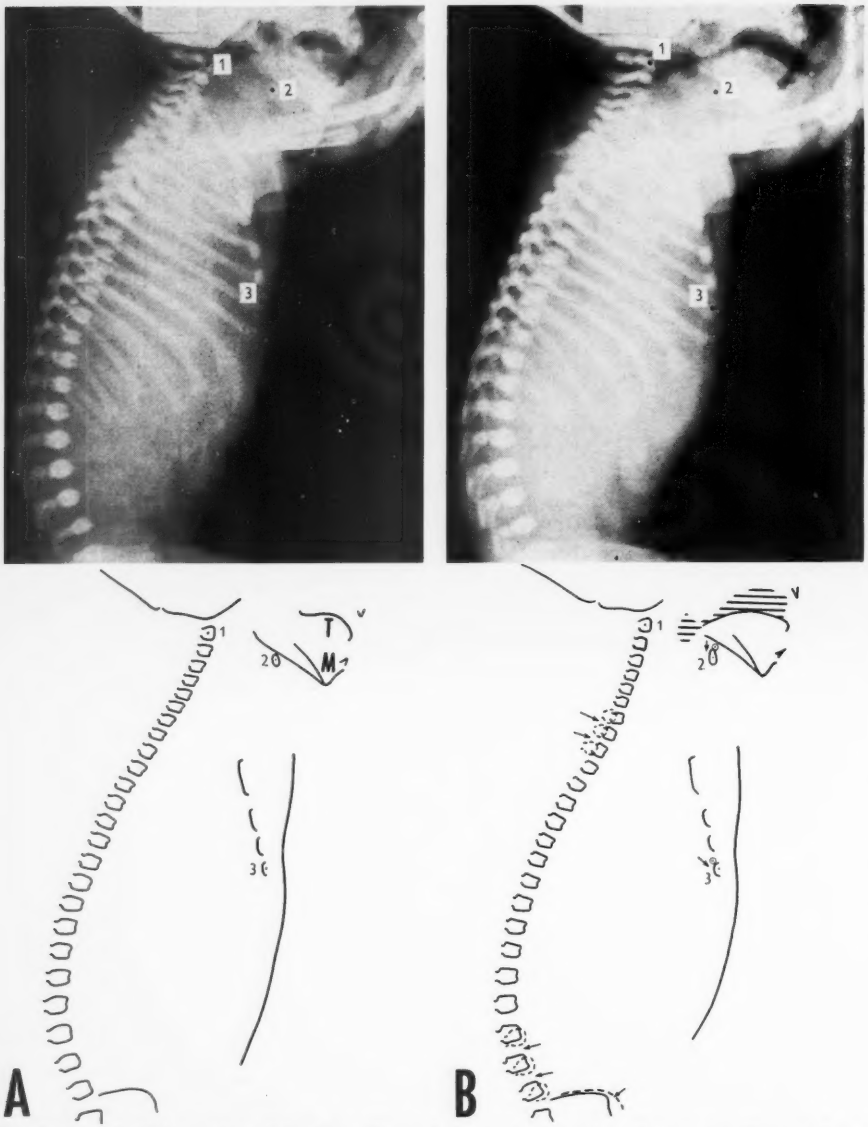
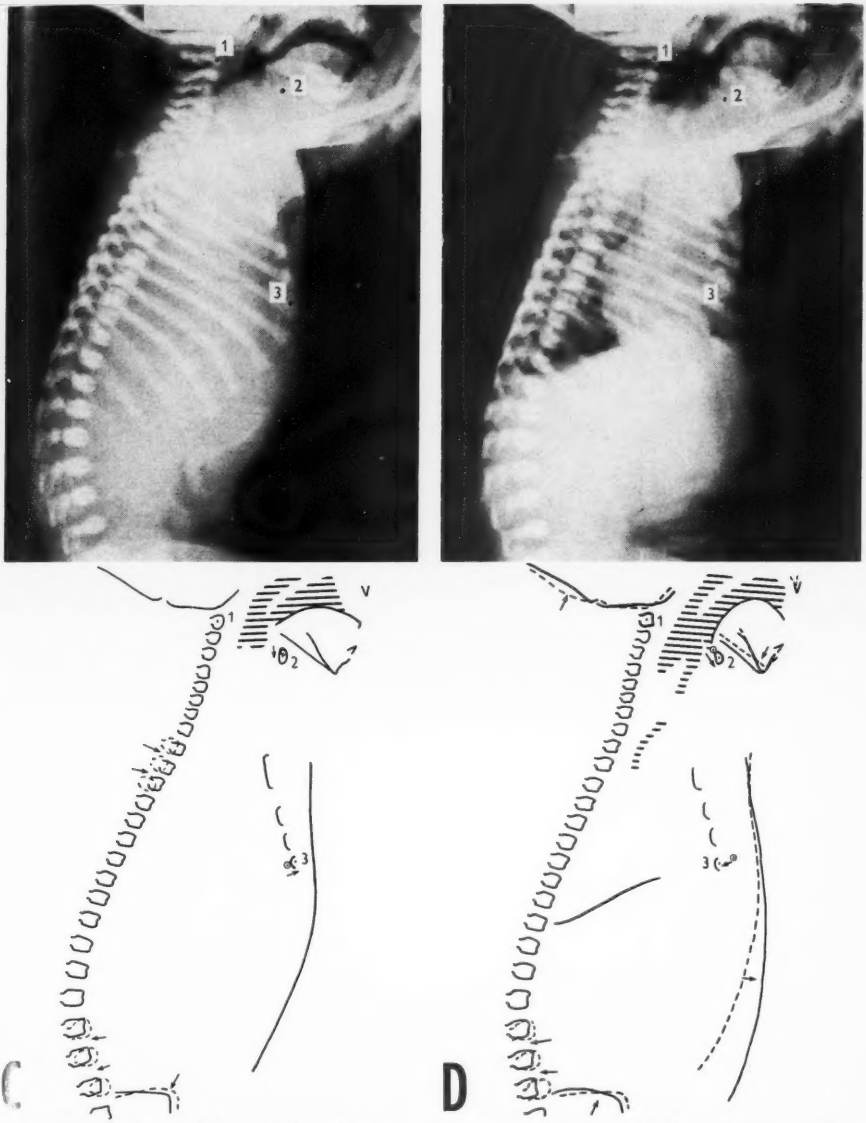


Fig. 2, *A–I*. Initial aeration of the lung. Glossopharyngeal respiration. Consecutive films at 3 p
second, beginning approximately 7 seconds after delivery.
A. No radiologically evident air in pharynx or in thorax. *B*. Aeration of the mouth is associate
with progressive caudad displacement of the hyoid (No. 2), in relation to odontoid process (No.
and to upper incisor tooth and tongue. There is also slight ventrad displacement of the upper thorac
and extension of the lower lumbar spine. *C*. Further caudad displacement of the hyoid. Also furth
ventrad displacement of the upper thoracic and extension of the lower lumbar spine. Dorsal wa
of the pharynx is displaced dorsally. *D*. An abrupt inspiration motion expands the pharynx an



thorax. The head is slightly extended, the mandible and hyoid displaced caudally. The lower sternum (No. 3) is retruded, the abdominal wall protruded, and the lumbar spine further extended. *E.* The hyoid and tongue rise, and the dorsal pharyngeal wall moves ventrad to occlude the upper pharynx. The lower sternum moves ventrad. *F.* The pharynx is entirely occluded. The ventral abdominal wall straightens and moves dorsally. The cervical portion of the trachea is enlarged. *G.* The pharynx is still entirely occluded. The lumbar spine extends. *H.* The pharynx is occluded. The hyoid and larynx (at the upper margin of the trachea) move ventrally. *I.* Expiration occurs, through the nose and mouth.

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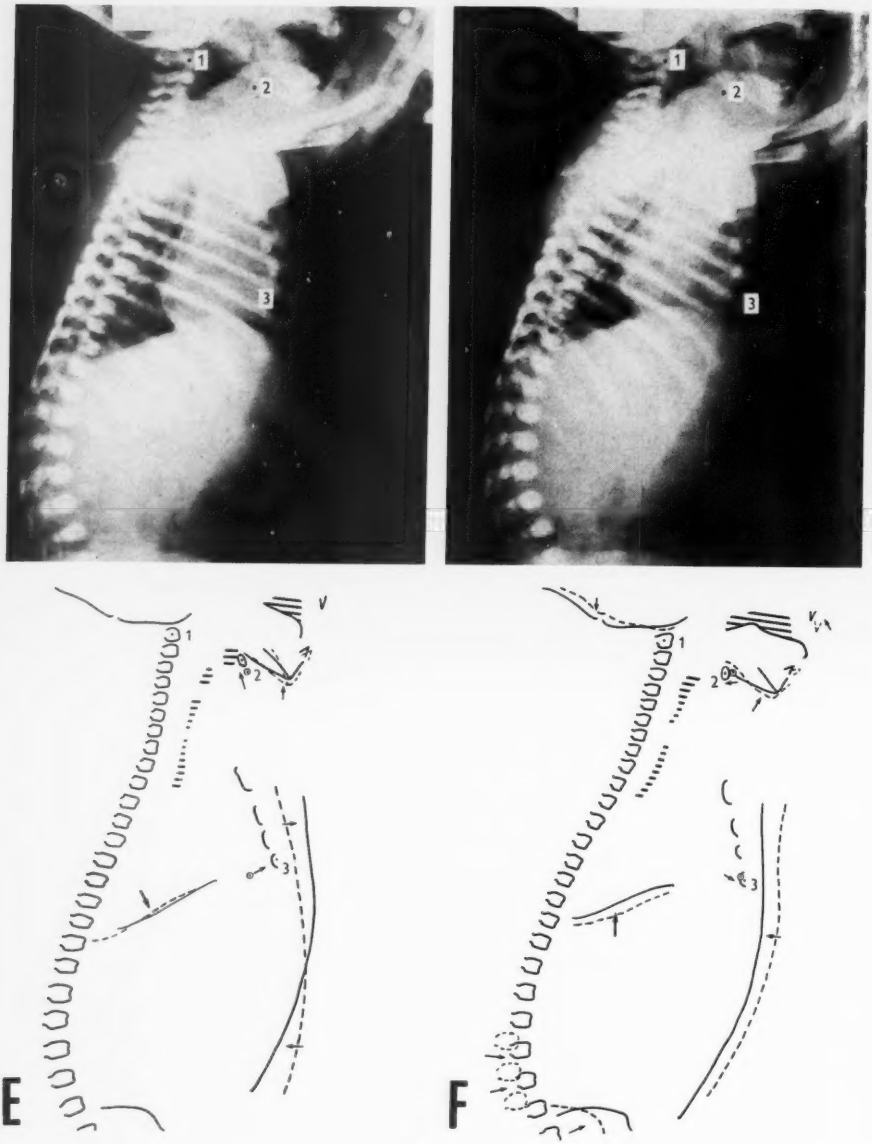


Fig. 2.

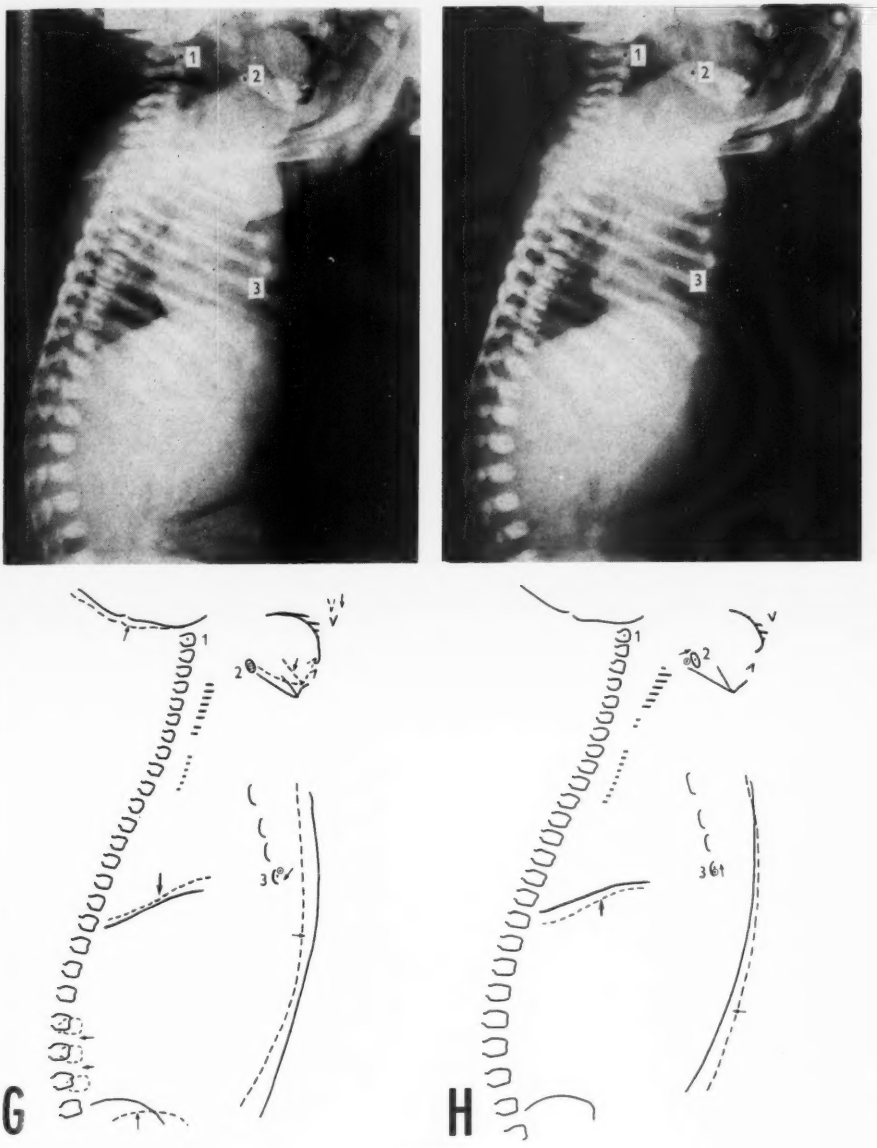


Fig. 2.

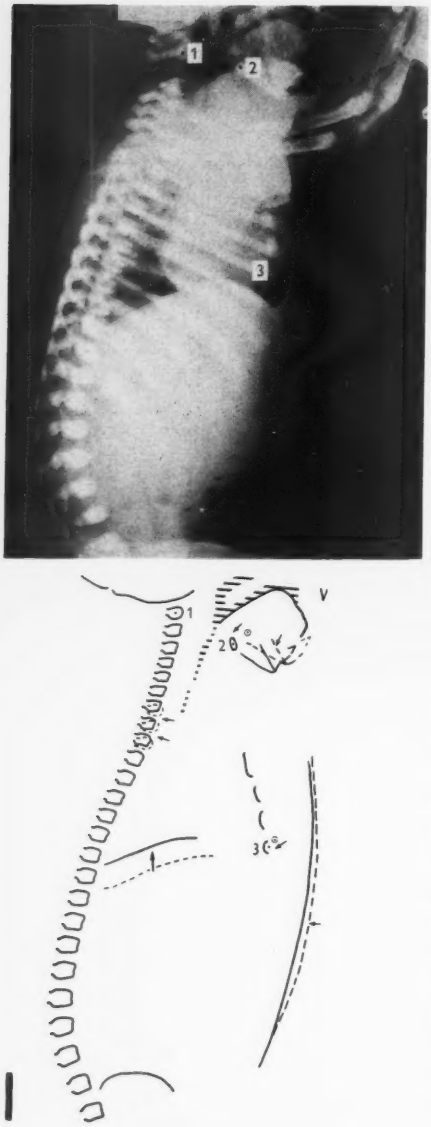


Fig. 2.

These pauses of static activity were noted in seven subjects, in whom they were 3 to 5 seconds in duration and occurred in various circumstances of air-filled pharynx, esophagus, trachea, or lung. They were noted in intervals between particular performances as well as at the occlusion climax of glossopharyngeal respiration or pharynx-larynx constriction. In one of these, an infant who had aerated his lungs prior to rapid placement upon the radiologic table, there was essentially no motion of the body axis, thorax, or pharynx region in 5 seconds of observations at 6 films per second. The possibility was suggested that the considerable sound and impact of the Schönander apparatus upon which the infant rested may have in some way occasioned these tonic arrests, as several of the infants cried immediately after cessation of the radiologic observation period, but no further indication of such a mechanism of arrest was obtained.

Initial Aeration of Airway.

The *initial penetration of air into mouth and into pharynx* might be associated with little discernible action or with slow action of the pharynx area. In one infant, the pharynx region was essentially unmoving but there was a slow increase in antero-posterior diameter of the thorax. Initial air-filling of pharynx might be associated with motions which were not of apparent physiological relation to this. As examples of this, in two infants (Figs. 3 *A* and 3 *B*; Figs. 6 *A* and 6 *B*), the dorsal portion of the tongue was transiently approximated to the hard palate and then withdrawn from it as air filled the pharynx. Motions of mandible and tongue indicative of sucking were found in coincidence with filling of the pharynx (Figs. 3 *C* and 3 *D*, and 3 *F* and 3 *G*). A "premonitory" demonstration of partial closure of the pla-

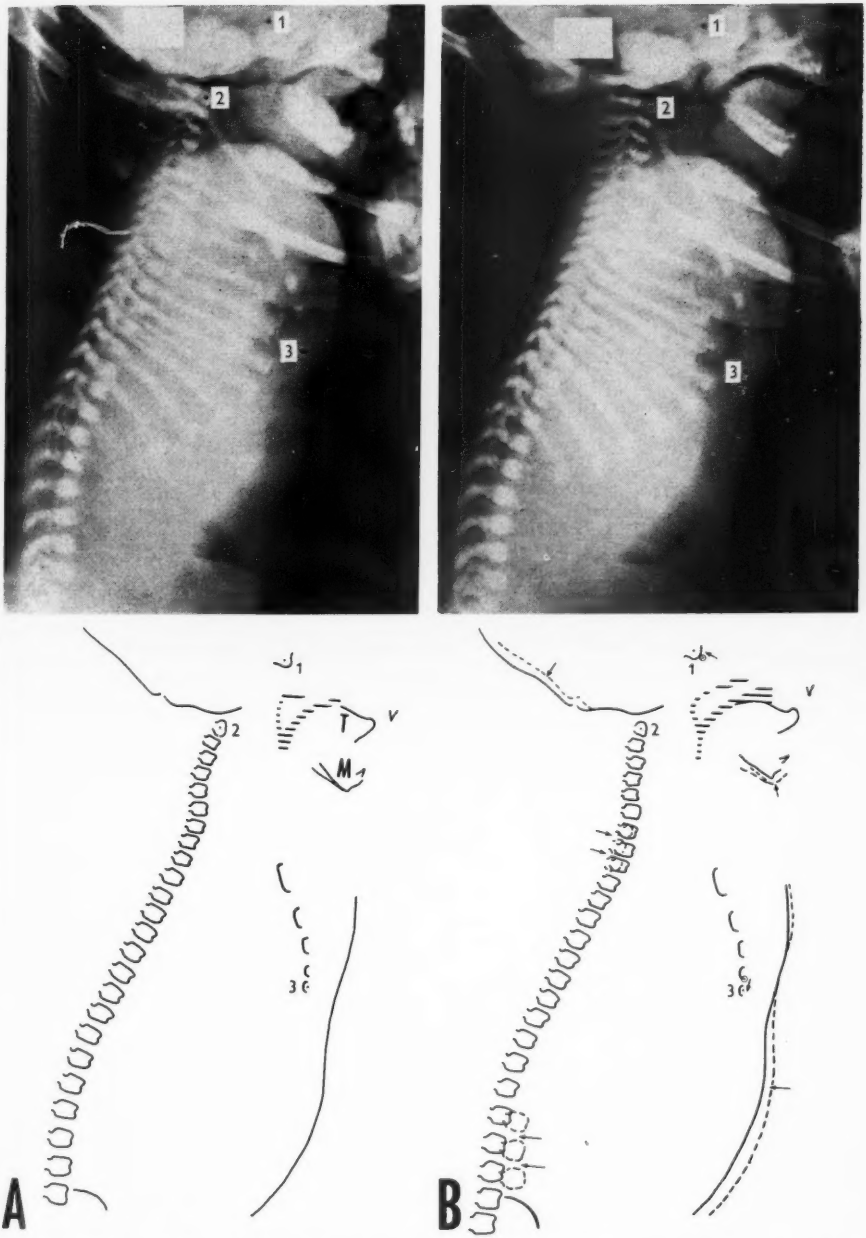
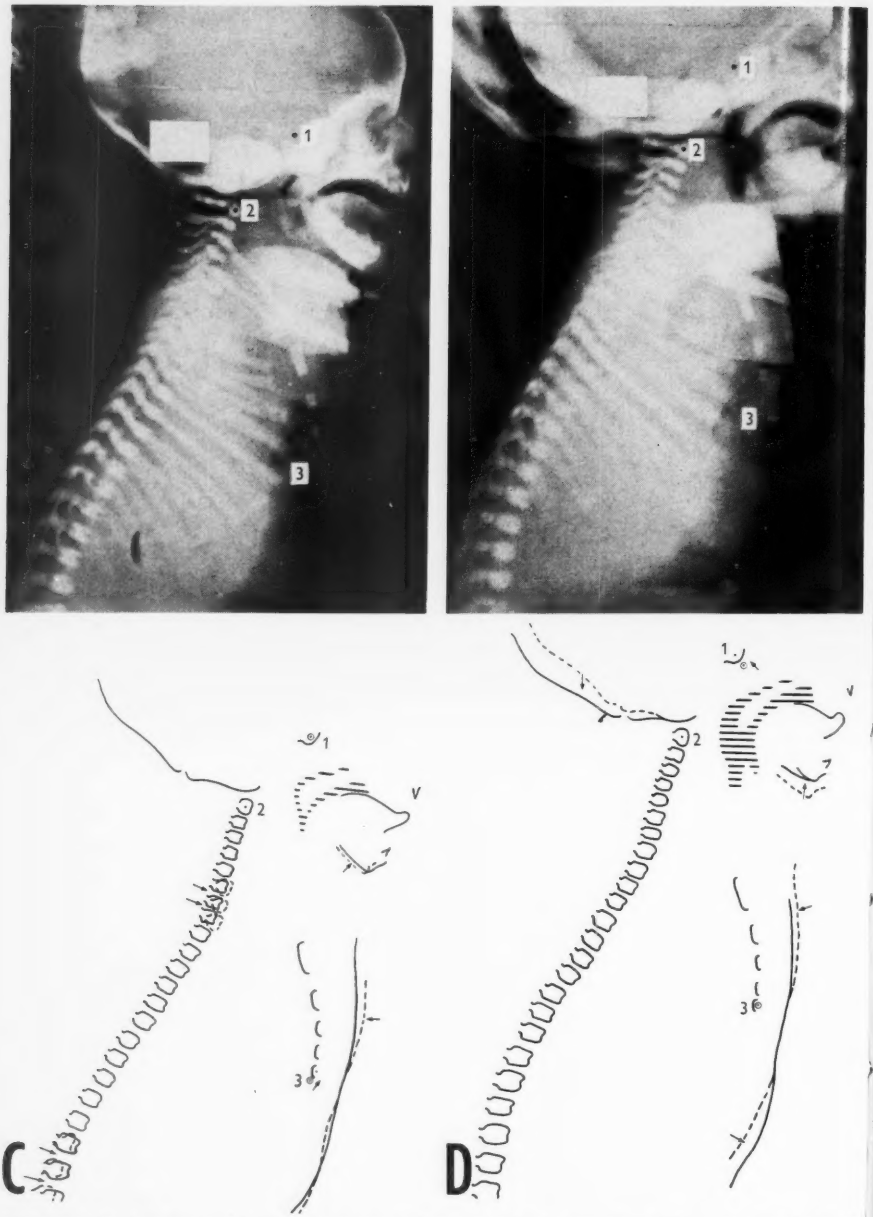
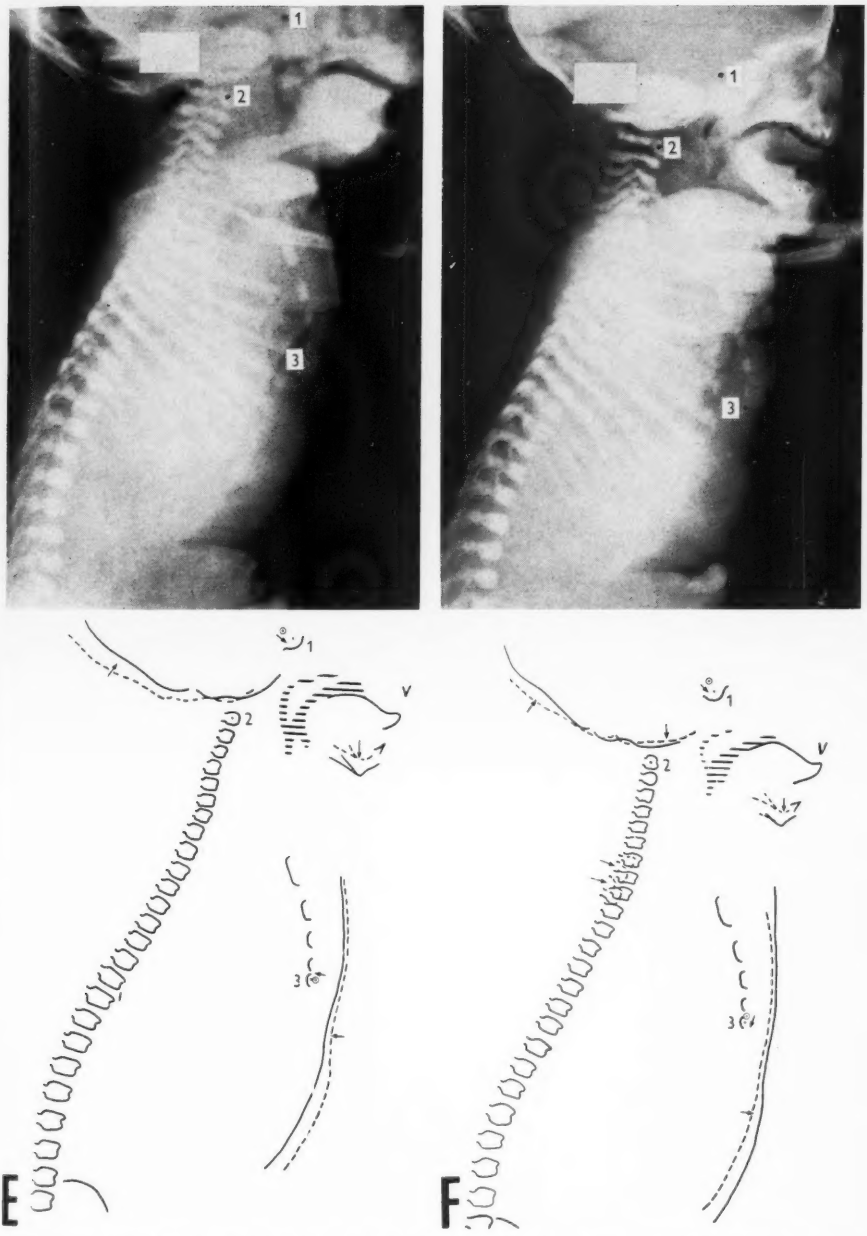


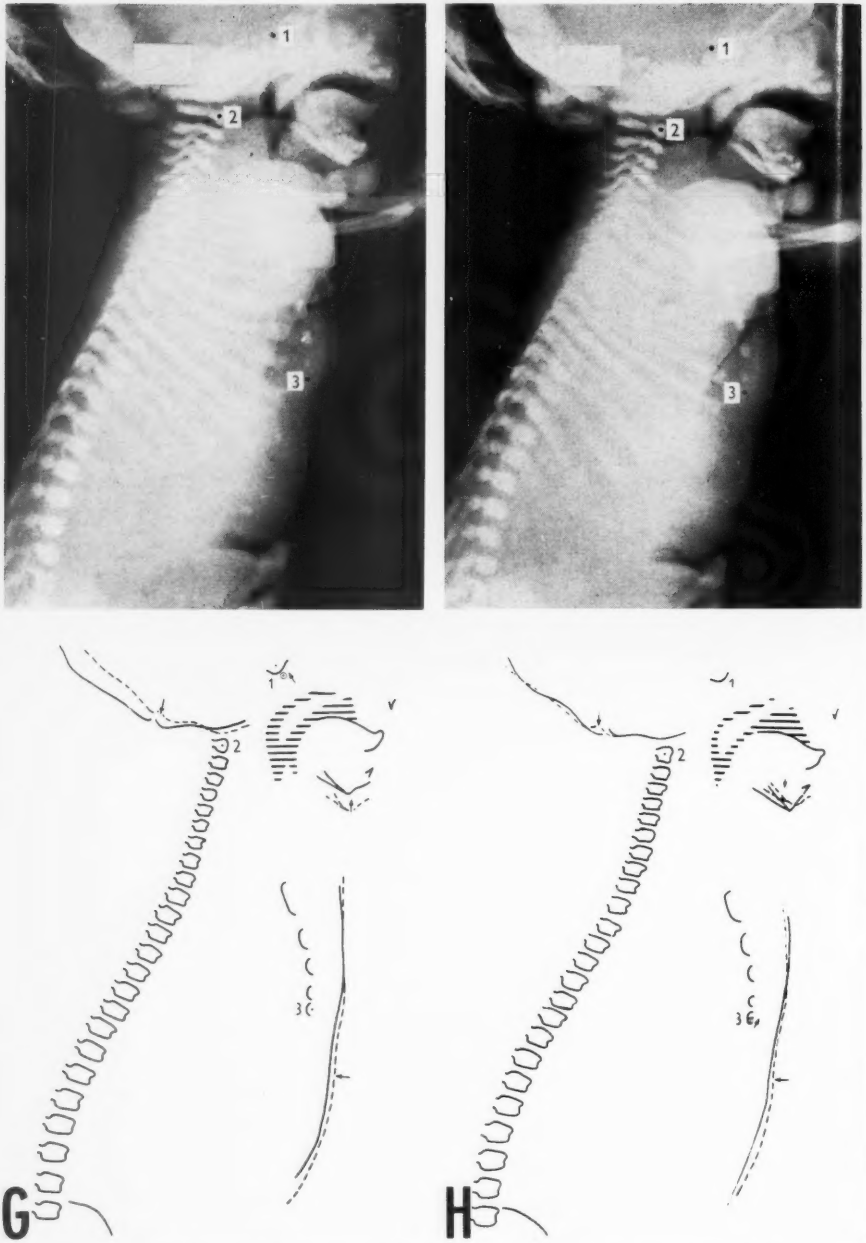
Fig. 3, *A–H*. Initial aeration of the pharynx. Films at 3 per second, beginning approximately 2 seconds after birth. This infant is also the subject of Figure 4. The hyoid is not identifiable. *A*. Minimal air in pharynx. Ventral portion of tongue pressed to hard plate. *B*. More air in pharynx. Slight flexion of head at neck, caudal displacement of sternum. Extension of lumbar spine.



C. Tongue further protruded. Slight motions of spine and of sternum. *D.* Pharynx expande in association with dorsal displacement of dorsal pharyngeal wall, extension at neck, and protru ion of the epigastrium.



E. Pharynx diminished. Motions of pharyngeal wall, mandible, head and epigastrium are the opposite of those in Fig. *D*. *F.* Protrusion of tongue.



G. Pharynx partially expanded in association with extension at neck. *H*. Similar to Fig. *G*.

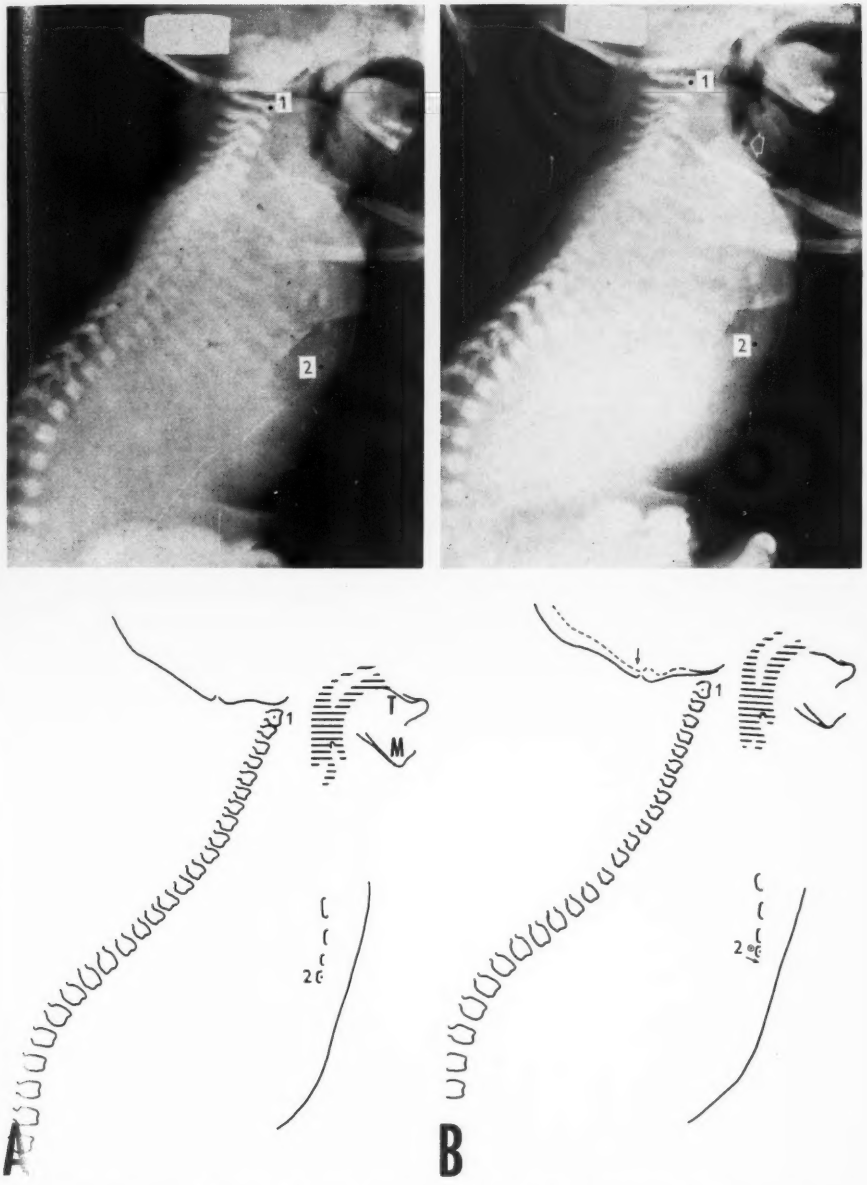
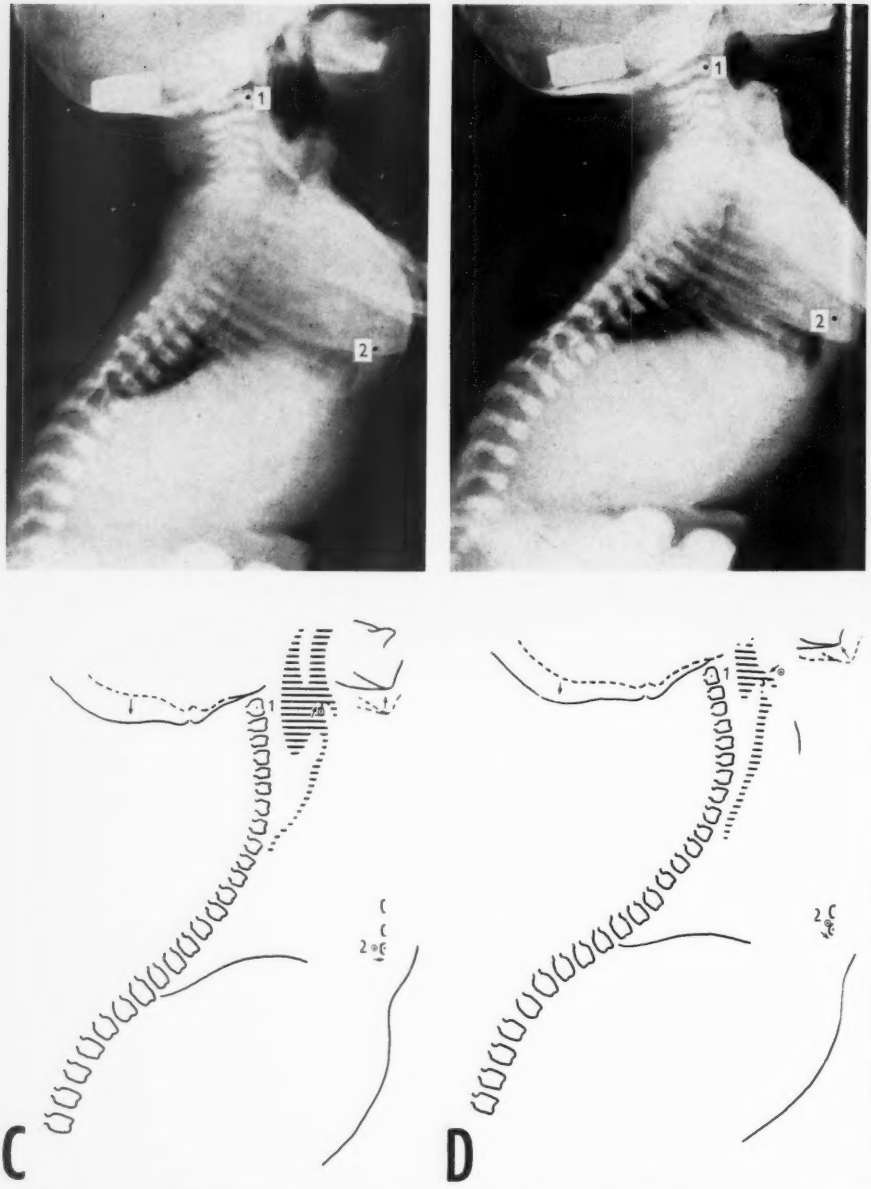
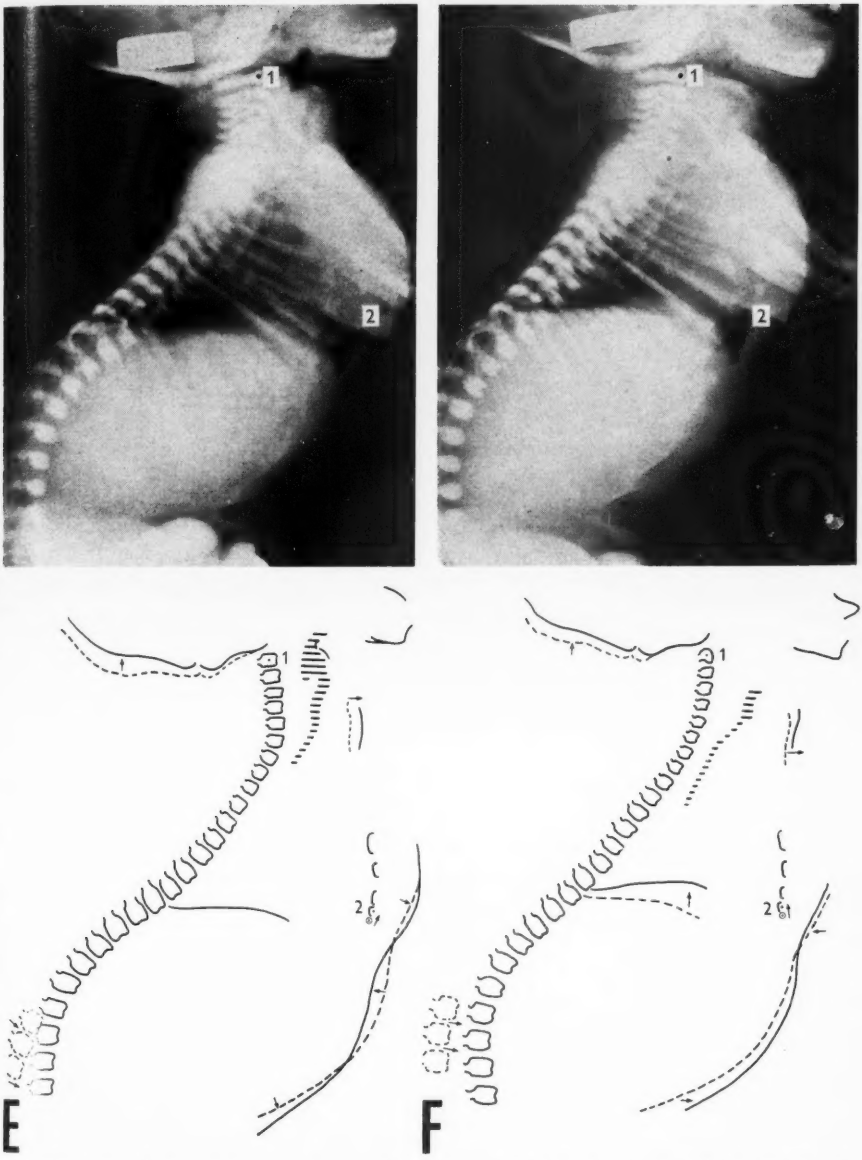


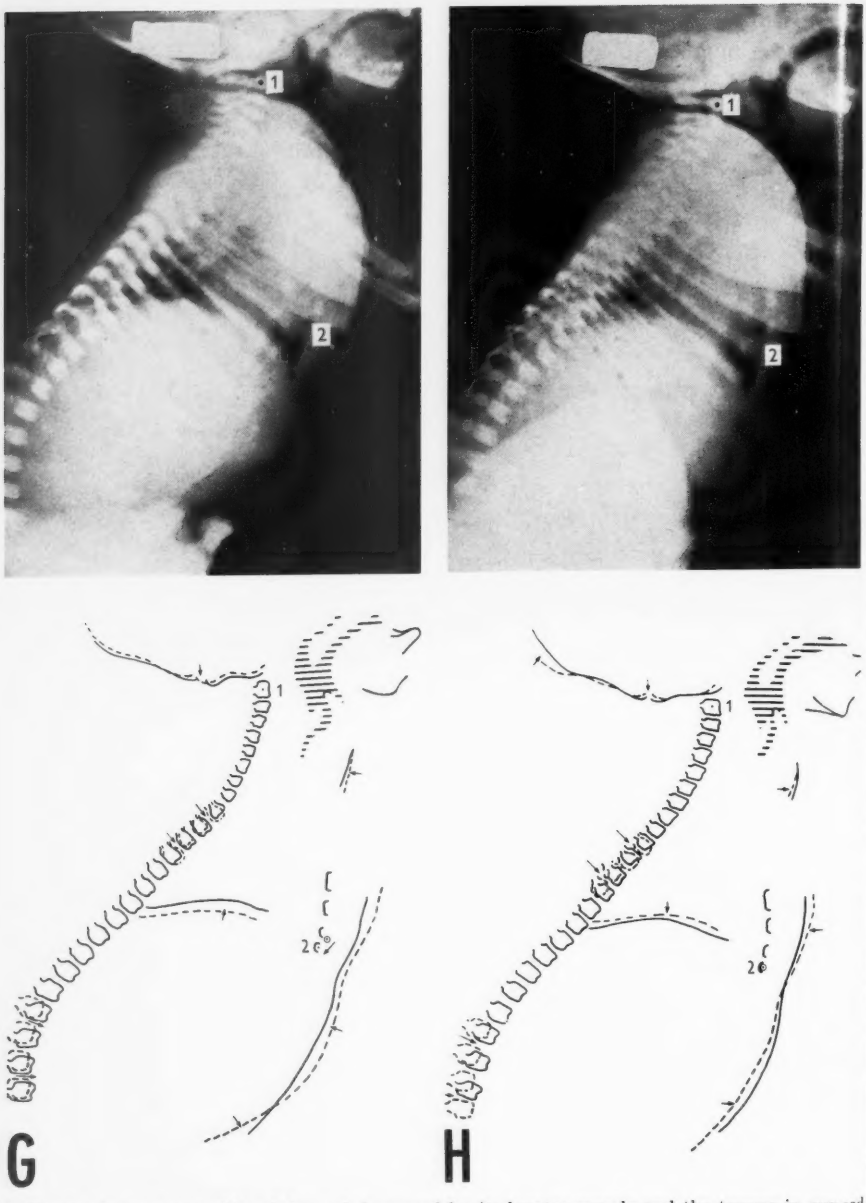
Fig. 4, *A–H*. Aeration of airway and lung followed by occlusion of the pharynx in glossopharyngeal pattern. This subject is the same as that in Fig. 3, the films taken 4 seconds later, at 3 per second. *A*. Slight increase in diameter of the pharynx in association with slight extension at neck. *B*. Further extension at neck and increase in diameter of pharynx.



C. Maximal expansion of pharynx and abrupt appearance of air in lungs in association with further extension at neck and with protrusion of the epigastrium in an inspiration contour. *D.* Occlusion of the epipharynx by ventrad displacement of the dorsal wall of the epipharynx, dorsal displacement of the palate, and dorsocephalic displacement of the tongue.



*E. A*dditional occlusion of the mesopharynx by further ventrad displacement of the dorsal pharyngeal wall and dorsad displacement of the tongue. The cervical portion of the trachea is slightly sino and the ventral margin of the neck, in the area of the suprasternal notch, is displaced ventrad. Begi ning of progressive lumbar flexion. *F.* Complete occlusion of the pharynx. The cervical portion of tl trachea is more sinuous, displaced further ventrad, and is in greater disproportion of diameter com ared with the thoracic portion. The ventral margin of the neck is displaced further ventrad. The diaphragm has moved cephalad.



G. Upper airway open with palate angled upward by its levator muscle and the tongue in cup ed contour, appropriate to cry. Displacements of sternum, ventral abdominal wall, and diaphragm appropriate to expiration. *H*. Same as Figure *G*, but with palate in apposition to dorsal pharyn eal wall.

rynx prior to complete glossopharyngeal performance is illustrated in Fig. 3.

Initial penetration of air into trachea from the pharynx might likewise occur without notable motion of mouth, pharynx, or larynx and without motions in the trunk which were distinguishable in these circumstances of observation. Conversely, in one infant, air failed to penetrate from the mouth into the larynx and trachea for 10 seconds despite considerable motions of pharynx region and of trunk.

Swallow of Air into Esophagus.

In most infants there was an active air-filling of the alimentary tract as well as the respiratory system within the immediate postnatal period (10). This swallow of air into esophagus was found to precede distinguishable appearance of air into trachea, bronchi, or lung in five of the infants of this series and in others it was found to be interspersed with actions of respiration. This swallow of air into esophagus entirely resembled swallow of bolus incidental to suckle feeding, although the volume of this "bolus" of air was relatively much larger. The pharynx was occluded in a cephalo-caudal sequence by the cephalically and dorsally displaced tongue and the converging pharyngeal walls. The hyoid moved principally in a cephalad direction. The larynx was closed by apposition of arytenoid mass to the epiglottis, and with anteroposterior expansion of the cervical portion of the esophagus into a funnel-like contour. This air contained in the esophagus was carried on variable schedule to the stomach, in which situation it usually became invisible, concealed by the radiodense mass of the liver.

Filling of Lung

In one infant, in whom films were taken at half-second intervals, air-filling of the lung occurred in two stages of inspiration coincidentally with expansion of the pharynx. In all 13 others in whom initial filling of the lung occurred during the roentgen observation period, there was complete or partial closure of the pharynx and larynx, inconstantly preceded by a phase of dilatation.

The motions of the pharynx region associated with initial aeration of the lung were in two major patterns. The distinction of these two patterns was that of the relative motions within the pharynx region to accomplish closure of the pharynx and larynx. One of these resembled the coordination of swallowing and was apparently the same action as glossopharyngeal respiration observed in an infant having repetitive glossopharyngeal respiration as a part of focal stem seizures (8), or this action occurring voluntarily in poliomyelitis patients with paralysis of the thorax (4, 5, 11).

The definitive general motions of glossopharyngeal respiration, like those of swallow, were cephalad ascent of the ventral pharyngeal wall, analogous to the engulfing type ingestion found in lower vertebrates. This was followed by an enclosing maneuver in which the pharyngeal portion of tongue, the palate, and the posterior and lateral walls of the pharynx participated. The other major pattern was one of complete or incomplete closure of the pharynx area, here termed "constriction", while the hyoid and larynx were held in essentially stable position, except for caudad or dorsad motions of lesser extent occurring late in the action. Rather, the

posterior and lateral walls of the pharynx moved in relation to this relatively stable motor reference composite. By this criterion, this category of respiration-relevant pharynx region performance resembled the larynx and pharynx modulations of respiration in speech. These patterns of motion of the pharynx were integrally related to those of the walls of the thorax concerned in these common efforts.

Glossopharyngeal Pattern of Motions

The definitive motions of occlusion in the pharynx region in glossopharyngeal pattern were inconstantly preceded by a phase of expansion of the lumen of the pharynx (Figs. 2 *C* and 2 *D*, 4 *B* and 4 *C*). This was evident in six of the seven infants of this series in whom glossopharyngeal respiration was clearly shown. This was variable in schedule, progressing slowly in some and within one-third second in others. There was also variation in extent of dorso-ventral and cephalo-caudal expansion. The hyoid body, larynx, and pharyngeal portion of the tongue were displaced ventrad and the dorsal wall of the pharynx was displaced toward the cervical vertebrae. A simultaneous initial aeration of the lung and exaggeration of expansion of the pharynx occurred abruptly in each of these infants. The air-expansion of the lung was associated with caudad displacement of the diaphragm and ventrad displacement of the sternum and the epigastrium: the familiar motions of inspiration.

In the glossopharyngeal pattern of occlusion of the pharynx, the hyoid was displaced principally cephalad and the tongue rose and approximated the palate, then protruded dorsally into the pharynx. The dorsal pharyngeal wall moved ventrad. The resultant occlusion of the pharynx was seen to progress in a cephalo-caudad sequence in those instances in which it is sufficiently slow that its graduation could be demonstrated by these methods (Figs. 2 *D*, 2 *E*, 2 *F*; Figs. 4 *C*, 4 *D*, 4 *E*, and 4 *F*).

If this motion progressed to complete occlusion of the pharynx, the vestibule of the larynx was likewise occluded and the air-outlined cervical portion of the trachea was expanded in anteroposterior diameters and its upper portion assumed a funnel-like contour, with the flat superior aspect of the funnel commonly in an oblique relation to the transverse plane. Particularly in occlusion associated with glossopharyngeal pattern, this lower margin of the occluded larynx was drawn into proximity to the hyoid body. At completion of this occlusion, the hyoid had completed its elevation. The ventral margin of the neck was in some subjects displaced ventrad in the area of the suprasternal notch (Fig. 4 *E* and 4 *F*). In association with the glossopharyngeal pattern of occlusion of the pharynx, the abdomen diminished in gross anteroposterior extent with flattening of the ventral abdominal wall and flexion of the lumbar spine, and the diaphragm was displaced cephalad (Fig. 2 *E* and 2 *F*; 4 *E*, 4 *F*, and 4 *G*).

A variation of the initial or preliminary expansion phase of glossopharyngeal respiration was that of associated motions of abrupt extension at neck and opening of the mouth. This was the gasp or "*Schnapper*" described by Schmidt (9). The extension at neck was noted in one infant of this series, with opening of the mouth (Fig. 4 *B* and 4 *C*). This extension was coincident with expansion of pharynx

and lung. Partial anteflexion at neck then occurred at the time of pharynx occlusion.

Another variation of this glossopharyngeal pattern was that of its incomplete manifestation. Pattern identification or classification of these lesser or partial manifestations depends upon criteria of their basic motion as exemplified by the displacements of the hyoid. This variation is illustrated in Fig. 5, in which the upper pharynx is occluded by cephalad displacement of the tongue, along with the hyoid (Fig. 5*B*). The succeeding film, at one-third second interval, shows the pharynx closing but principally by ventral displacement of the dorsal wall, rather than in the cephalo-caudad sequence seen in examples of complete manifestation of performance in this pattern.

Pharyngeal Constriction

The other actions of the pharyngeal region as it participated in initiation of respiration were related to the more familiar patterns of respiratory modulation. They were characterized by stability or by dorsad or caudad displacement of the hyoid. Constriction or occlusion at pharynx and larynx were essentially by discrete motion of the tongue, arytenoids, palate, and pharyngeal walls in relation to the stable supporting musculature converging upon the hyoid (see Fig. 1*B*).

In motions of this constriction pattern, there was more commonly a gradation of degree. The maximal effort occluded the entire pharynx and larynx, as illustrated in Figs. 6 and 7. This occlusion might be preceded by an abrupt inspiratory expansion of airway and lung (Fig. 6*D*), and with or without extension at neck (Fig. 7*B* Motions of the abdominal wall appropriate to expiration occurred during this occlusion (Fig. 6*E*).

The discrete motions of the pharynx and larynx associated with stability of the hyoid or with its dorsal or caudad displacement during initiation of respiration are essentially those which are seen throughout postnatal development. The palate was most commonly in curved contour and positioned diagonally in the pharynx, intermediate in distance between the tongue and the dorsal pharyngeal wall (Figs. 8*B*, 9*B* and 9*F*). With expansion of the pharynx, the palatopharyngeal folds were brought into prominence (Figs. 6*D* and 6*F*). A discrete ridge occasionally protruded from the dorsal pharyngeal wall at the insertion of the palatopharyngeal folds (Fig. 7*A*). The common pattern of deflection of the expiratory air stream to oral portal was that of slight dorso-cephalad displacement of the curved palate, to approximate the dorsal pharyngeal wall (Figs. 10*A* and 10*C*). But the palate might be angled into a foot-like contour by traction of its levator muscles and in this contour be displaced dorsally to the pharyngeal wall. In Figs. 8*A* and 8*D*, this approximation is illustrated in incomplete and in complete form, respectively, with a discrete epipharyngeal ridge protruding in proportion to the displacement of the palate.

The most varied motions in this region were those of the tongue. The extent and directional variety of its mobility were best shown in performances in which the hyoid was stable or but slightly displaced. Its simplest motion was that of cephalad displacement, in a "humped" contour to approximate the area of the junction of the hard and soft palate (Fig. 8*D*).

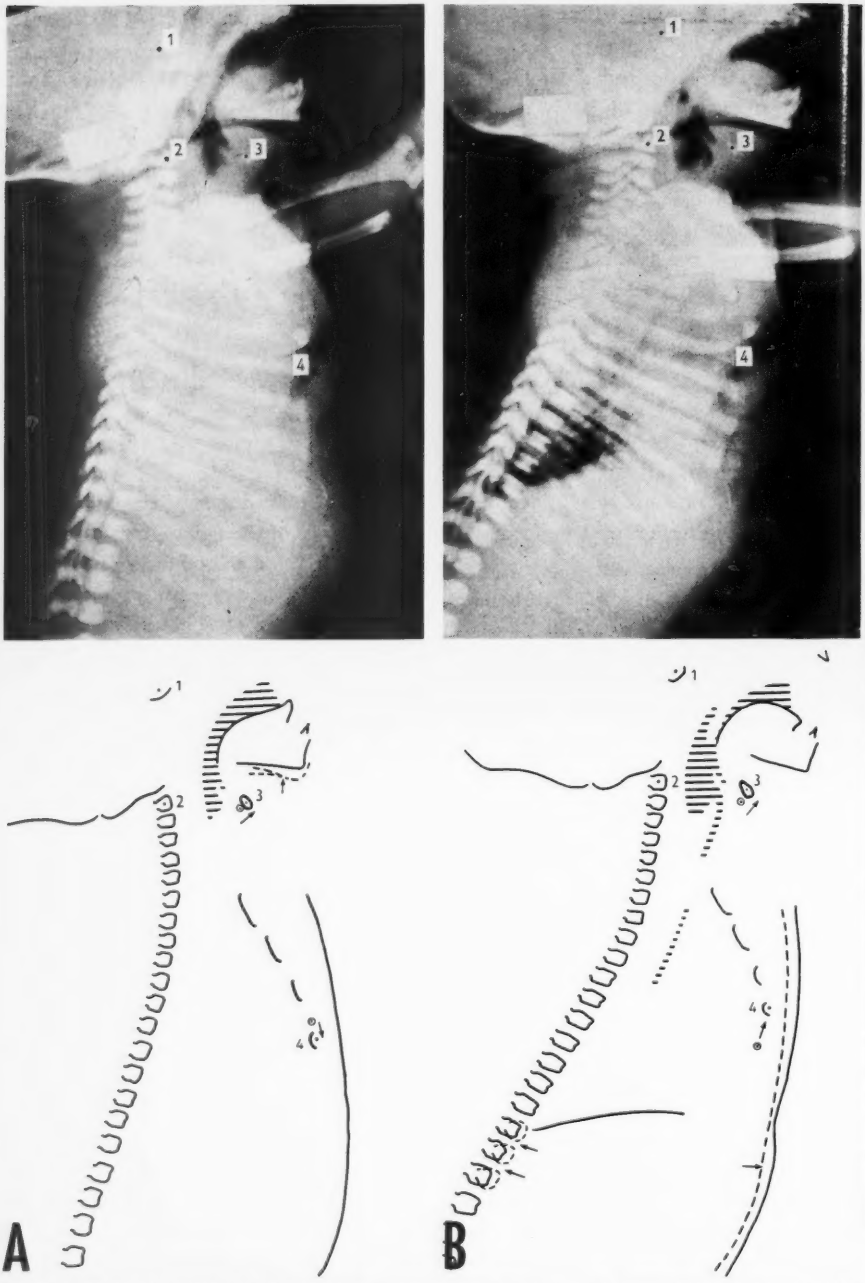
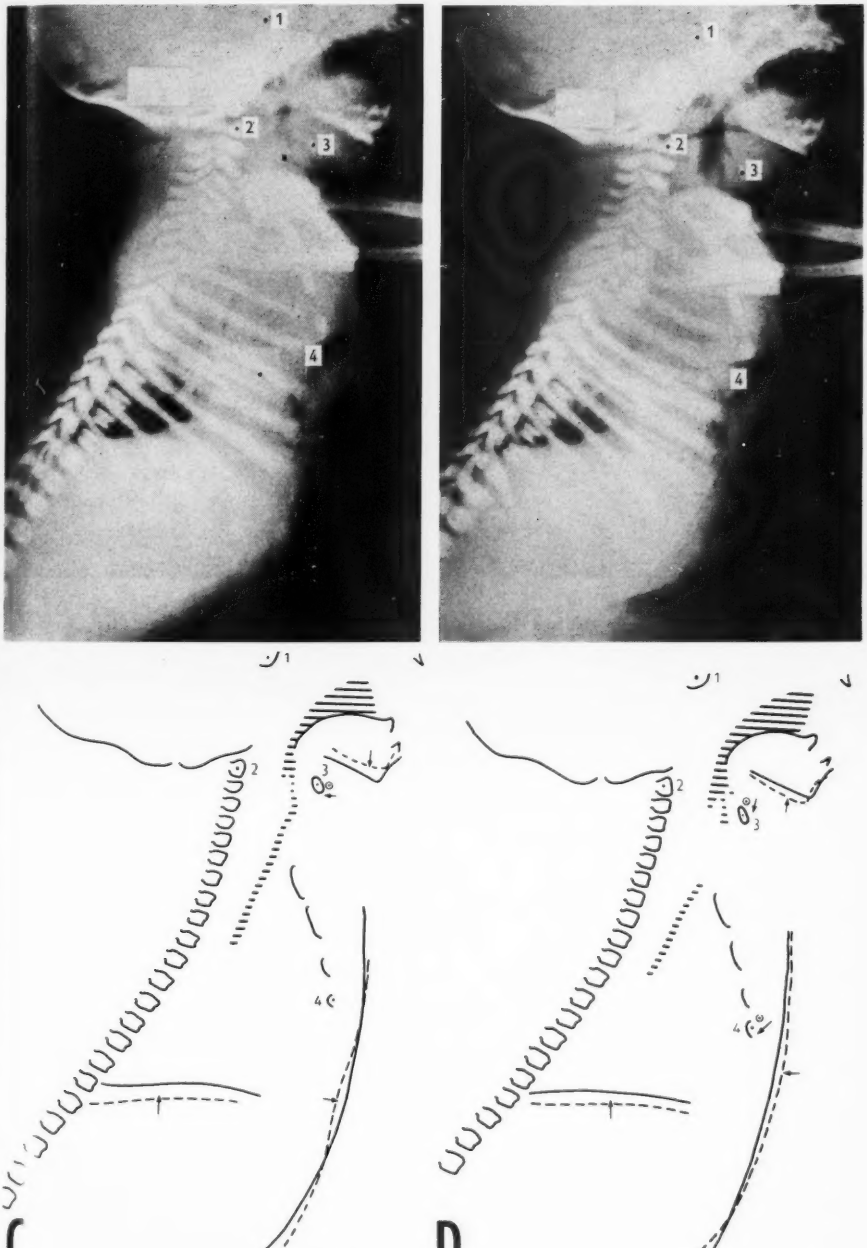


Fig. 5, *A–D*. Partial occlusion of the pharynx, apparently in pattern of glossopharyngeal respirati n. Films at one-third second, beginning 7 seconds after birth. *A* Air in pharynx, but grossly abs nt from thorax. *B*. Mesopharynx expanded. Air in trachea and lung. Dorsal portion of tongu e is elevated to approximate palate. Hyoid displaced cephalad.



C. Narrowing of the pharynx, accomplished principally by ventral displacement of the pharyngeal wall. Arytenoid (indicated by short bar) and epiglottis approximated, leaving only a narrow laryngeal vestibule. Tongue and hyoid moved slightly dorsad. Flattening of abdominal wall and elevation of the diaphragm. *D.* Airway open. Motions of expiration in abdominal wall, sternum, and diaphragm. Hyoid descends to original position.

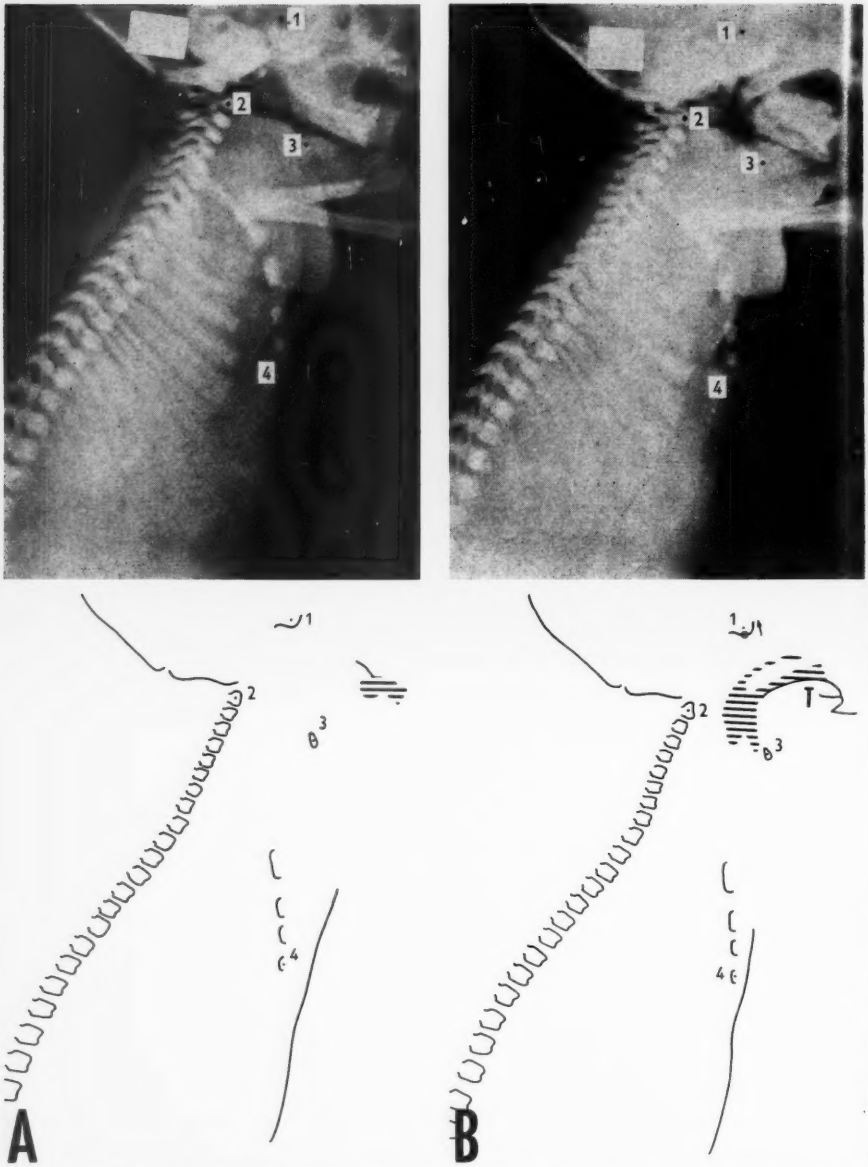
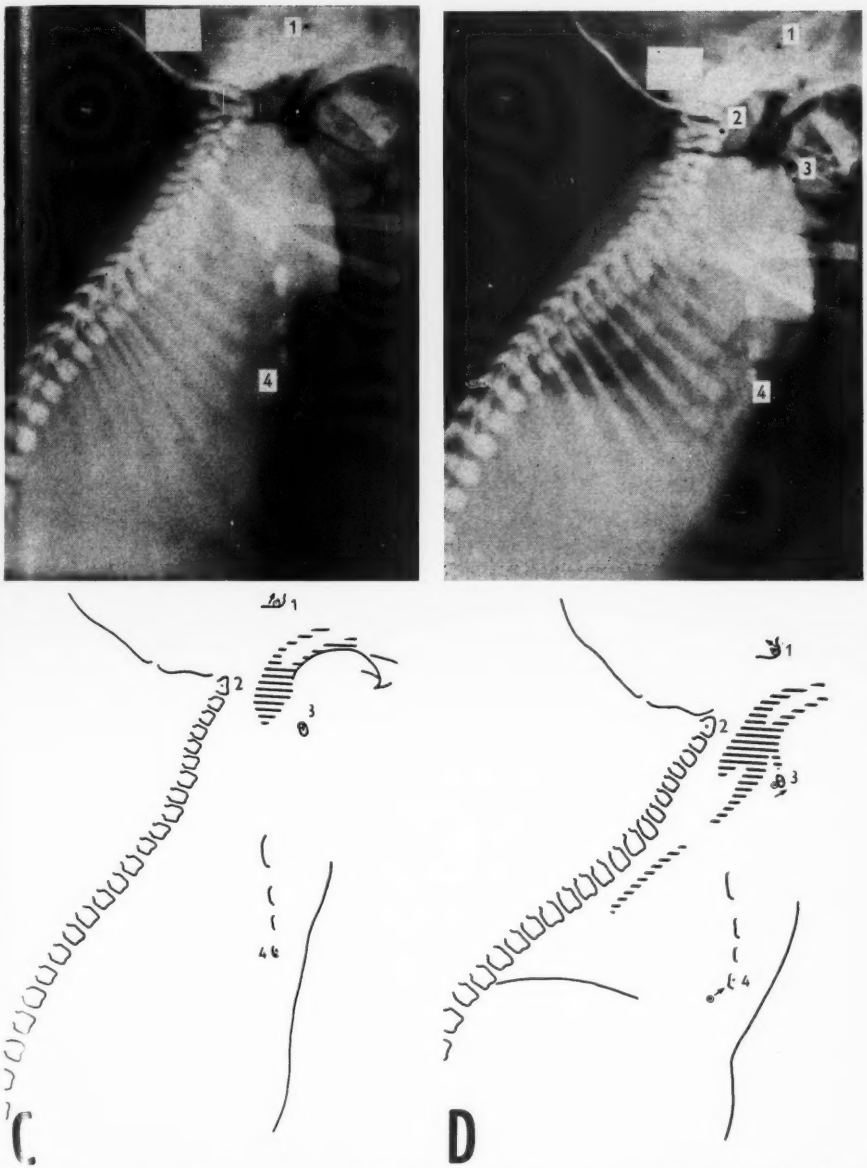
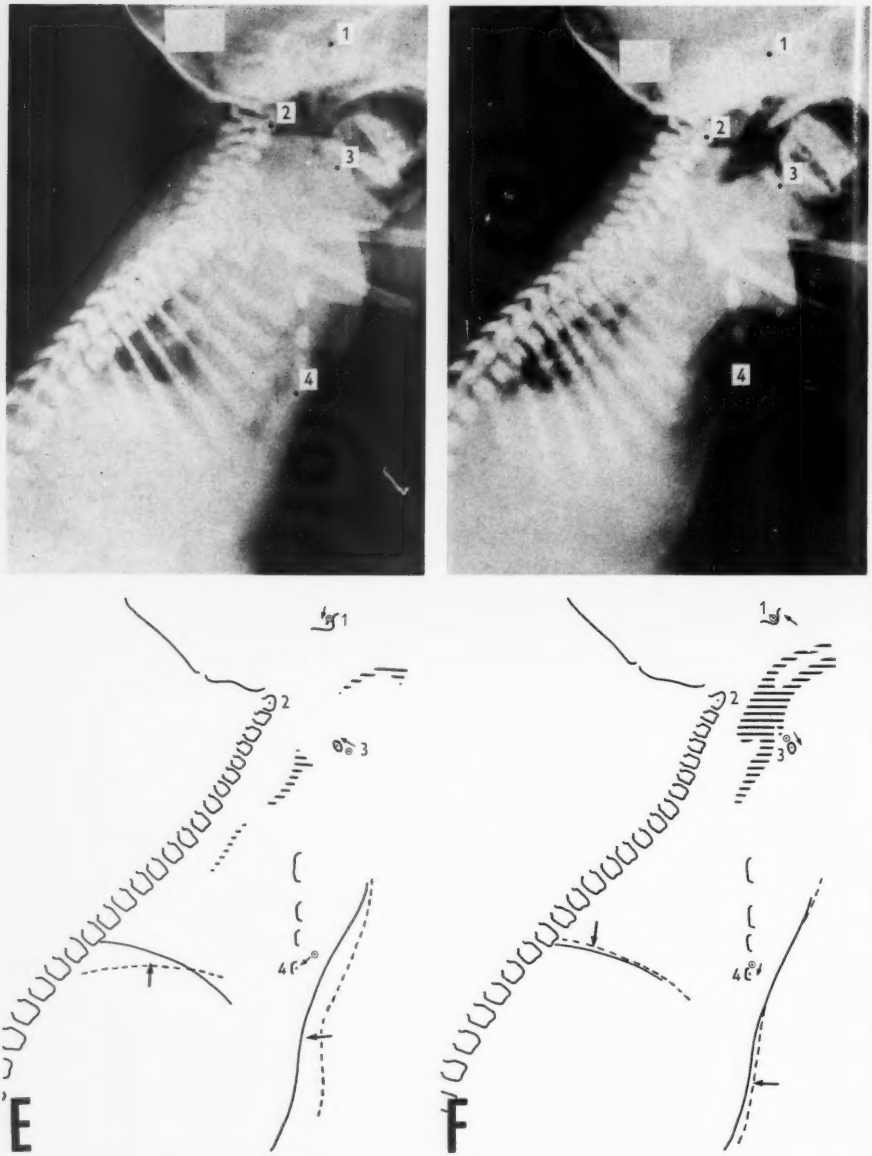


Fig. 6, *A–F*. Initial aeration of pharynx. Abrupt expansion of airway and lung, followed by closure of pharynx and larynx in a "constriction" pattern. Films at 2 per second beginning 1 second after birth; interval of 2 seconds between *A* and *B*. *A*. Initial filling of pharynx with air as the tongue withdraws from contact with palate. Air penetrates the laryngeal vestibule (adjacent to hyoid, No. 3). *B*. Tongue displaced further ventrally and caudally.



C. Air-filled cavity of pharynx elongated. Hyoid and sternum moved caudad. Air displaced from laryngeal vestibule. Tip of tongue dropped toward floor of mouth. The palatopharyngeal folds extend diagonally caudodorsad from the end of the palate. *D.* Expansion of pharynx in vertical and transverse diameters. Tongue is in humped contour, hyoid moves slightly ventrad. Air in lungs and epigastrium is protruded in inspiration contour.



E. Larynx occluded. Hyoid and conus are moved dorsad. Lower sternum is moved dorso-caudad and the protrusion of the ventral wall is diminished. *F*. Airway is re-opened.

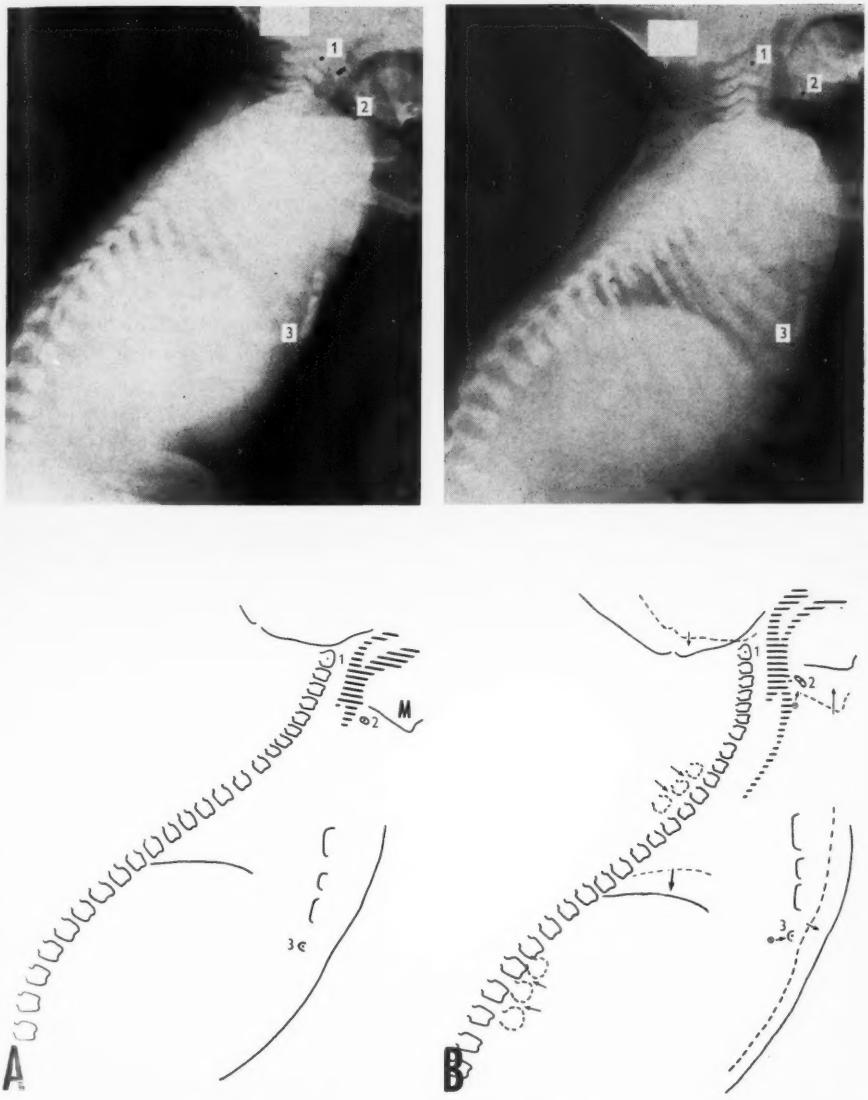
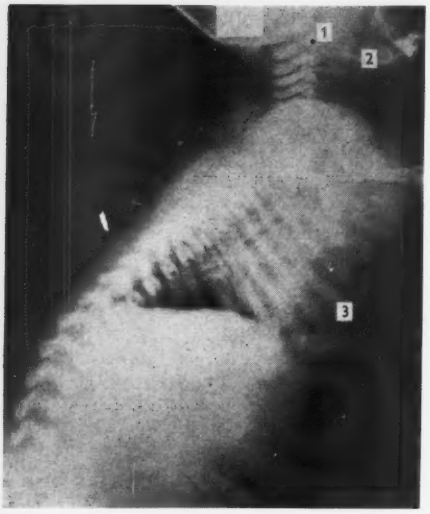


Fig. 7, *A–C.* Inspiration followed by pharynx occlusion in "constriction" pattern. Films obtained at 2 per second, beginning 5 seconds after birth. *A.* Air in pharynx, outlining palatopharyngeal fold and a discrete ridge protruding from the pharyngeal wall at the insertion of the folds (indicated by ba). Air grossly present in lung. *B.* Extension of head at neck with corresponding cephalad displacement of the hyoid and mandible. The tongue is displaced dorsocephalad in relation to hyoid, assuming a humped contour. The pharynx is elongated cephalocaudally. Air is increased in the lungs in association with inspiratory motions of lowering of diaphragm, extension of lumbar spine, ventro- cephalad displacement of the sternum, and ventrad displacement of the epigastric wall.



C. Occlusion of the pharynx in association with dorsal displacement of the hyoid and of the conus.

The dorsad motions of the tongue were combined with the cephalad motions, as a variety of modulations of a fundamental dorsocephalic rolling action upon the stable or slightly moving hyoid base. By these actions, the tongue contributed with the palate and pharyngeal wall to closure of various portions of the upper pharynx, but a cephalocaudal progression of occlusion, like that of glossopharyngeal respiration, was not observed. The most extensive rolling action of the tongue in these respiratory or "pharynx constriction" patterned performances is that in cry (12) in which the tongue arches dorsally and then caudally, and does not approximate the dorsal pharyngeal wall.

The tongue is also the principal mover of the epiglottis. The epiglottis is anchored inferiorly on the thyroid cartilage and enclosed within the arch of the hyoid bone. When the airway is open the under-surface of the epiglottis is directed approximately toward the tip of the palate. As the tongue rolls dorsally in modulation of respiration or in swallow, it moves the epiglottis dorsocaudally. The diameter of the vestibule is determined also by the mass of the arytenoid cartilages and the soft tissues and mucosae which cover them. This "arytenoid mass" appears radiographically in continuity with the dorsal wall of the hypopharynx; the hypopharynx is collapsed except during expansion of the pharynx (Figs. 6*D*, 8*B*, and 8*C*). During the ex-

Fig. 8, *A–D*. Partial occlusion of the pharynx in constriction pattern with initial aeration. *A*. Pharynx in moderate expansion. Air in length of trachea. Palate is elevated and minimal epipharyngeal ridge is discernible (at arrow). *B*. Further expansion of pharynx and small amount of air in lung. Inspiration contour of ventral wall of trunk.

C. Pharynx slightly diminished. Tongue cephalad. Hyoid unmoved. More air is apparent in lung. *D*. Tongue further cephalad, approximating palate. Palate cephalodorsad, approximating discretely protruding epipharyngeal ridge (at arrow). Lower portion of laryngeal vestibule and the area of the vocal cords occluded without evidence of ventricle. Upper trachea broad and in conical contour. Hyoid slightly dorsad. Abdominal wall straightened.

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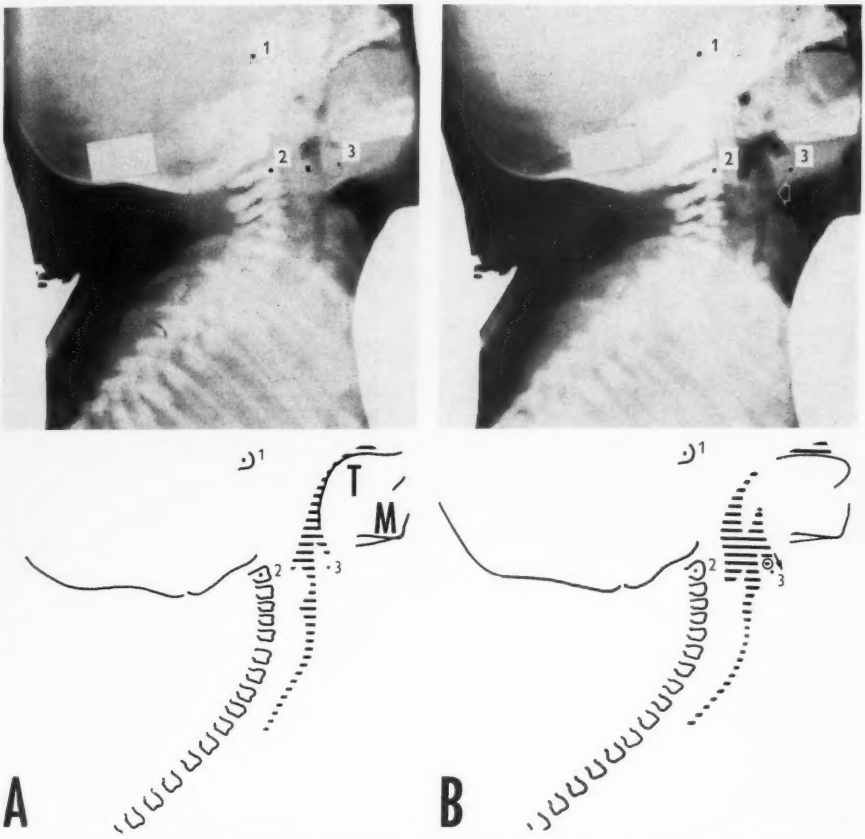
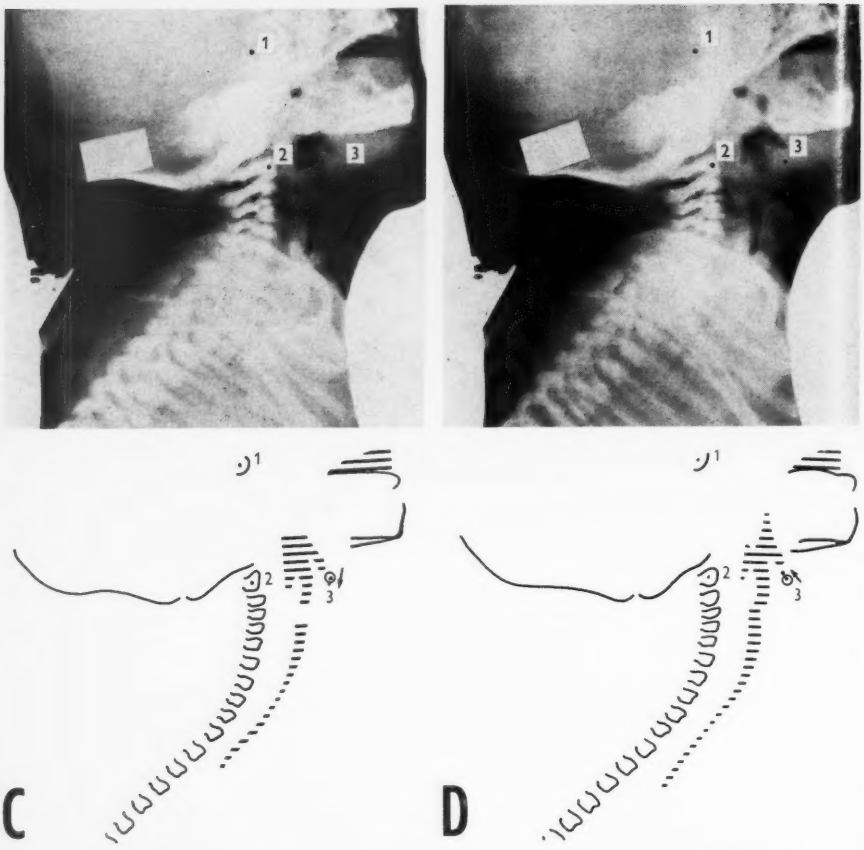


Fig. 9, *A–F*. Actions of pharynx and larynx in constriction pattern with initial aeration. Films consecutive at 6 per second, beginning approximately 1 second after birth. *A*. Initial aeration of airway. Larynx open, arytenoid mass (indicated by short bar) closer to epiglottis. *B*. Expansion of pharynx and of laryngeal vestibule. Approximation of tongue to hard and soft palate. Hyoid moves slightly ventrocaudad. Laryngeal ventricle is apparent (at arrow).

pansion of the pharynx, the laryngeal vestibule may increase also, as the arytenoid mass remains intermediate between the displaced dorsal pharyngeal wall and epiglottis (compare *D* and *F* of Fig. 6, or *A*, *B*, and *C* of Fig. 10, or all portions of Fig. 9). The arytenoid mass may move independently to accomplish closure of the vestibule by apposition to the epiglottis (Fig. 9*E*). Medialward displacement of the true and false vocal folds is demonstrated commonly by a prominent laryngeal ventricle (Fig. 9*B* and *F*). Closure of the true vocal folds by their median apposition is not discernible by this radiographic method. But closure in the region of the false cords is well demonstrated as the upper margin of the funnel-shaped air lucency of the upper trachea in occasions of larynx occlusion. This is illustrated in coincidence

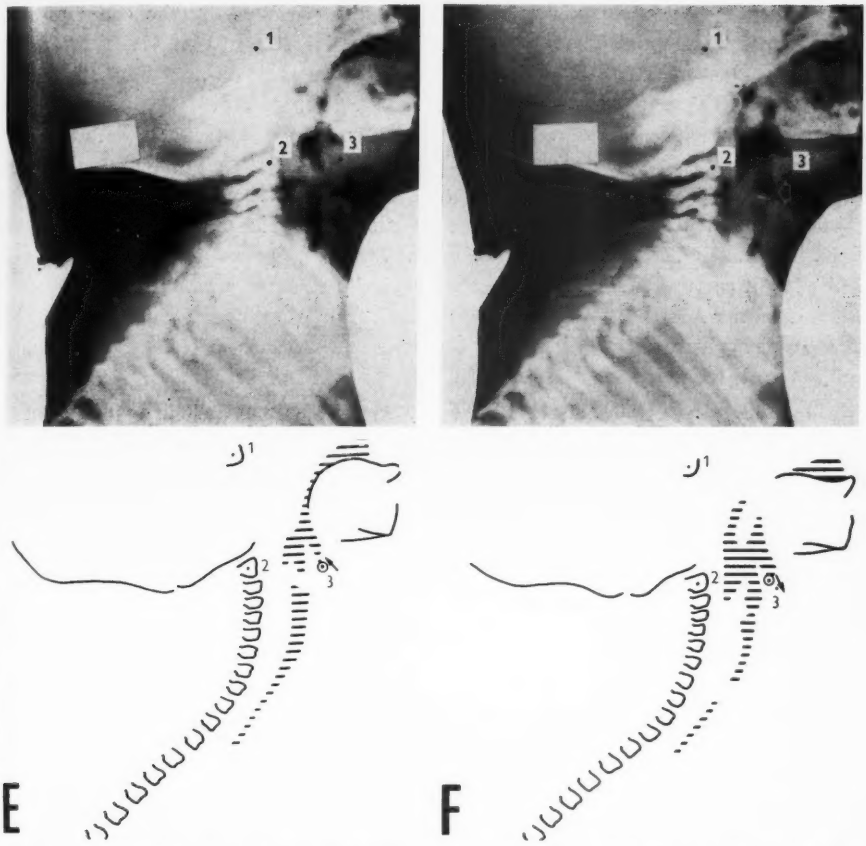


C. Upper pharynx occluded by dorsally displaced tongue and approximation of palate to dorsal pharyngeal wall. Hyoid moves ventrad minimally. Air grossly present in lungs. *D*. Pharynx slightly larger.

with closure of the vestibule in Fig. 8 *D*, and with vestibule open in Fig. 9 *F*.

These discrete motions are at times fairly rapid, as discrimination is commonly associated with rapidity in other pharynx and larynx coordinations, such as speech (13). This variety and rapidity is illustrated in Fig. 9, of successive radiographs obtained at 6 per second during initiation of respiration, beginning approximately 2 seconds after birth. These rapid changes in the pharynx and larynx are probably imposed upon slower respiration. Thus, in Fig. 9 *E*, the pharynx is small and open to the mouth with the trachea broad, while the larynx is closed. In the next radiograph the pharynx is expanded and the trachea small.

The pharyngeal wall was also continuously active in these infants, but always



E. Pharynx open to mouth. Arytenoid displaced ventrad, approximating epiglottis. Hyoid position is essentially unchanged. Lower portion of laryngeal ventricle closed. Cervical trachea broad. *F*. Pharynx again expanded. Trachea comparable to Figs. *A–D*.

in coordination with the other pharyngeal structures of palate and tongue. This radiographic method demonstrates only the displacements of the dorsal portion of the wall, but this may safely be considered representative of the motions of the pharyngeal wall generally. Irregularity of dorsal withdrawal of the dorsal wall during initial aeration of the pharynx was demonstrated in Fig. 3, showing a protrusion at the level of the middle constrictor muscle. The discrete epipharyngeal bar noted in the dorsal wall at the level of the elevated palate and the protrusion at the insertion of the palatopharyngeal folds have been mentioned previously. This method of observation of respiration-relevant activity of the pharynx gave no clue to varied activation of the inferior constrictor, which is attached to the

larynx, for the hypopharynx was closed except for partial opening during pharynx expansion (see above).

The wall of the epipharynx and mesopharynx moved generally in tidal respiration (Fig. 10) and in the exaggeration of inspiration preceding pharyngeal closure in glossopharyngeal or compression pattern (Figs. 2, 4, and 5). These motions of the wall were in coordination with oppositely directed motions of the tongue (Fig. 10) or, if respiration was by nasal portal, of the apposed tongue and palate. These general motions of the pharynx were noted only at slower rate, in coincidence with respiration. The extent of these general motions of the pharynx with tidal respiration are remarkable, compared with the smaller excursions of the pharyngeal walls in older subjects even with effortful respiration (14).

Discussion

It is apparent from these radiographic observations that the whole of the respiratory organization is involved in initial aeration of the lung and establishment of respiration. At this critical physiological transition of respiration, the infant has available motor actions of the upper respiratory way which perform in integration with the respiratory actions of the trunk. The upper respiratory way appears to be continuously in action throughout this transition. Specific motions occur against a background of static activity, which activity is evidenced by the contours and the spatial relations of the palate and larynx when respiration was apparently arrested. These studies give further description and specification of the "postpartum pause" described by Higgins (15). This static activity is apparently the prologue of the mechanism of maintenance of the pharyngeal airway during physiologically mature respiration (14).

Each of these performances associated with initiation of respiration gave evidence of generalized activity in the pharynx region. *Glossopharyngeal respiration* demonstrated the larger ranging motions of the intrinsic and the supporting pharyngeal musculature that characterize swallow of air or food. In the other major pattern of respiratory action, *pharyngeal constriction*, the motions were potentially also large and accomplished an extent of occlusion which was apparently peculiar to the small infant, but the structures of the pharynx and larynx moved in relation to the comparatively unmoving reference structures of the hyoid bone and the thyroid cartilage. Each of these actions is a neonatal respiratory adaptation of the basic performances of swallow and of respiration, respectively. These adaptations of the upper airway are essentially physiological supplementations contributing to this occasion and circumstance.

These supplementations were principally and most distinctively actions of the pharyngeal region. There was parallel action within the trunk but it was less

Fig. 10, *A–D*. Variations in pharynx with tidal respiration. Films obtained at 2 per second beginning approximately 15 seconds after birth. *A*. Pharynx moderately expanded. Chest in expiration contour. *B*. Pharynx moderately expanded. Chest in inspiration contour. *C*. Pharynx diminished. Chest in expiration contour. Arytenoid mass (at short bar) is displaced ventrally, narrowing the laryngeal ventricle. *D*. Pharynx moderately expanded. Chest in inspiration contour.

2
1
3
2
1
3
B

1
2
3
C
D

conspicuous and also not distinctive from common postnatal respiratory motions, by these methods of observation. Thus, the glossopharyngeal action was initiated by expansion of the pharynx, and this expansion of the pharynx might occur more than one time before the exaggeration of expansion in the pharynx and thorax which immediately preceded the swallow-like occlusion of the pharynx. And this occlusion might be associated with expiratory motions within the trunk. The corresponding associated participation of pharynx region and trunk in "pharyngeal constriction" was simply that of coincidental compression of the trunk in motions appropriate to expiration.

These performances have their definitive elements in the pharynx region. This region is distinctively capable of the varied and complex performances of feeding and of respiration and also of control of their interactions. These interactions of feeding and respiration are physiologically familiar. In fish, the respiratory stream of water is carried over the gills by swallow-like actions of the pharynx (16). In certain of the amphibia, the lungs are inflated by swallow action (17). In mammals, there is a transient arrest of respiration, and possibly a slight inspiration (*Schluckatmung*) early in the swallow action (18, 19) which is linked to the swallow in central nuclear regulation (18).

The abrupt and simultaneous distention of pharynx and thorax immediately preceding the pharyngeal occlusion phase of "glossopharyngeal respiration" is a phenomenon which has not been observed before. In the repetitive "glossopharyngeal respiration" observed in respiratory-paralyzed poliomyelitis patients (20) or in an infant having focal brain stem seizures (8), the airway is continually valved in alternation with the upper pharynx or the larynx. In the glossopharyngeal respiration observed in newborns there is an initial phase of active expansion of the pharynx which in six infants preceded evident aeration of the lung. In the singly-occuring "glossopharyngeal respirations" described herewith, there is apparently an abrupt and forcible inspiration associated with distention of the pharynx. Parallel distention of pharynx and lung in lesser degree was seen in later breaths (Fig. 10). Thus, we see evidence of an integration of action of pharynx region and trunk in their expansion as well as in their parallel constriction.

It is apparent that following delivery of the infants of this series, there is no restrictive or consistent sequence of activation of the total respiratory mechanism, or of associated motions of body axis, mouth, or limbs. This study demonstrates a variety of actions which are manifestations of either of two major patterns of performance of the pharynx region, and the externally evident motions of the human infant at birth are related to these pharynx area actions. The visibly most conspicuous respiratory relevant maneuver, of extension at head and neck commonly combined with opening and closing of the mouth, described by Schmidt (9) and by Peiper *et al.* (21, 22), are inconstant correlates of the action of expansion of the pharynx.

The common element of these maneuvers in which the upper respiratory way participates is that of transient enclosure of air within the thorax, an enclosure at the pharynx and larynx which may be

complete or partial. In some instances of this closure, as in Figs. 4 *E* and 4 *F*, there is indication of an increase in intrathoracic pressure. These radiologically indicated changes in intrathoracic pressure require elucidation by other methods. It will be necessary to converge additional methods of observation upon the newborn infant, supplementing roentgenograms, to determine the intrasomal flow and pressure variations associated with initial aeration of the lung and of the alimentary tract. The studies here reported indicate a precaution in such observations, in that they should not interfere with the normal physiological function of the pharynx and larynx area incident to their obtaining. Thus, catheters penetrating the pharynx, larynx, and esophagus may possibly interfere with normal function of these organs at this time. It is also apparent that many of the definitive studies of the role of the upper respiratory mechanisms in initiation of respiration must be accomplished in other mammalian species, preferably those which most resemble the human in these mechanisms.

These performances of the upper airway should also be included in common clinical evaluation of respiratory performance of the infant at birth. They are barely discernible by external observation, but the method of cervical auscultation distinguishes adequately between swallow, glossopharyngeal respiration, the abrupt sounds of opening and closing of the upper airway, and the higher-pitched sounds of partial occlusion. This method is now in use by the writers.

At our present stage of clinical understanding, we are dependent upon apparently random manifestation of these upper respiratory phenomena. But it may be safely inferred that these phenomena are specifically and uniquely elicited, though the mechanisms of their elicitation are still unknown.

Summary

1. The whole of the respiratory organization is involved in the initial aeration of the lung and establishment of the respiration.

2. The pharynx region may perform distinctively at this time in an engulfing action ("glossopharyngeal respiration"), the motions of which are highly similar to those of ingestion of bolus into the esophagus.

3. The more familiar respiratory modulations of the upper airway are also in action at this time, performing in relation to a comparatively stable hyoid base. These respiration-patterned motions may result in closure of the whole of the pharynx or discrete closure of portions of the pharynx or the larynx.

The mechanisms of elicitation of these varied actions of the upper airway, their immediate motor mechanisms, and their effect upon pulmonary ventilation require further investigation.

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Glossopharyngeal Respiration as a Part of Focal Seizures of the Pharyngeal Area in an Infant[1]

by JAMES F. BOSMA[2]

This report is concerned with repetitive glossopharyngeal respiratory (GPR) movements occurring as a part of focal medullary or pharyngeal-laryngeal seizures in an infant one month of age. The phenomenon is observed visually, by auscultation, and by cinefluorography.

This is undescribed previously as a form or associated manifestation of seizure. It is also a significant clinical example in that it is an additional circumstance of demonstration of the motor phenomenon of GPR, different from its voluntary elicitation for respiration purpose in respiratory-impaired poliomyelitis patients (1), and its occurrence in the transition of the newborn human infant to autonomous pulmonary respiration (2, 3).

Clinical Summary

This girl infant was born at estimated 10 months of gestation. At 6½ months of pregnancy, the mother had "influenza" of 3 weeks duration, complicated in its latter portion by otitis media. At estimated 7 months the mother was moderately acutely ill for one day and had a rash; three weeks later, her children had a similar rash and she concluded without further medical diagnosis that this was "German measles". She had "false labor" in irregular but increasing episodes beginning in the seventh month of gestation; there was no associated vaginal release of blood or amniotic fluid. True labor began spontaneously and was completed on normal schedule and without obstetrical incident.

The infant was considered normal in her immediate neonatal period and her parents particularly recall that she cried strongly within a few minutes of birth. She was initially fed at breast and later on a cow's milk formula, and demonstrated no impairment of initiation or continued performance of suckle feeding. On the sixteenth postnatal day she had evidences of a mild upper respiratory infection, as indicated by increase in nasal secretions; her mother at this time had a severe respiratory illness. On the twenty-fourth day the infant had a severe coughing episode when attempting to swallow a small amount of aspirin suspended in water. Coughing and choking episodes thereafter continued in increasing incidence and severity until on the thirty-second day these graduated to cyanosis and unconsciousness of a few minutes' duration. These seizures were apparently precipitated by cough, or occurred spontaneously at borders of sleep.

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They did not interfere with feeding but might occur after completion of satisfactory feeding, perhaps as the infant was graduating toward sleep. These seizures were of 1 to 2½ minutes' duration and during the more severe episodes the parents alertly noted an appearance of "tightening" in the anterior cervical and submental areas. During the more severe seizures, there was mild opisthotonus or a slight rightward turning of the head and up-turning of the eyes. In intervals between seizures the infant continued to be alert and vigorous. She suckled well without choking. Cry was reported to be normal.

At our initial observation, on her thirty-ninth day of age, the infant was found to be entirely well-formed, in normal physical proportions, and in good state of nutrition and hydration. Contours of cranium, face, and cervical area were entirely normal. No distress was elicited by firm compression of the cranium or on passive motions of head and neck. The general contours of face, anterior mouth, and tongue were normal. The pharynx was also normal per satisfactory inspection, employing an infant laryngoscope. There were no distinguishable abnormalities in the thorax, abdomen, pelvis or limbs.

The infant was alert, responsive, and roused or subsided from rousal in a normal manner. She gave good visual and auditory attention. Coordination of the eyes, upper and lower face, muscles of mastication, tongue, and pharynx were entirely normal. Suckle, swallow, and cry were normal. Musculature of neck and trunk was of normal volume and passive mobility, and posture motions were normal for this age. Gross motions of arms and legs were normal. Biceps and patellar reflexes were moderately and symmetrically increased and plantar reflexes were symmetrically in extensor pattern. Routine hemogram, urinalysis, and fasting blood sugar, calcium, phosphorus and phosphatase were normal.

Roentgenograms of the cranium, face, and cervical spine demonstrated no abnormality. An electroencephalogram demonstrated essentially normal patterns in waking and sleep, with occasional sharp waves of variable distribution in the area sampled by standard cranial and ear leads.

Disturbance of the infant incident to examination elicited episodes of cry graduating abruptly into complete respiratory obstruction, with continuation of phrenic efforts of respiration. These were of two minutes duration or slightly longer, and were associated with severe cyanosis and generalized motions of disturbance without distinct opisthotonus or up-turning of the eyes or seizure demonstrations in the limbs. As the infant was left untouched, she relaxed toward unconsciousness and limpness and the milder phrenic respirations which continued were then effective in accomplishing respiration.

Dilantin sodium® was given orally in increasing dosage to 130 mg/day and the seizures were reduced to a few mild, non-cyanotic episodes each day. These partially controlled seizures could be elicited by tactile stimulation of the posterior wall of the mesopharynx and consisted of occlusion of the upper respiratory way of 10–20 seconds duration, followed by gulping motions recurring periodically at approximately 1½–2 second intervals. These were associated with little or no motion of the mandible or change in head-neck position.

By auscultation at the larynx, these began as a gurgling sound, graduating into a prolonged, loud, high-pitched squeezing sound which continued until the end of the current gulping effort. The duration of these sounds was 1–1½ seconds and the interval between these successive gulping efforts was very brief. Phrenic respiratory motions continued during these series of gulping actions. There was no hyperpnea at the end of these episodes, when normal thoracic respiration was resumed. These motions of the pharynx area were observed cinefluorographically and found to resemble the voluntary repetitive GPR of postpoliomyelitic patients having severe disability of thoracic respiration, as this phenomenon was observed cinefluorographically by Dail *et al.* (4), and by Ardran *et al.* (5).

In the succeeding three weeks, it was possible to reduce Dilantin medication to 50 mg/day while retaining adequate control of seizures. In the succeeding 12 months the infant was reported to have been nearly free of seizures and to have shown satisfactory neurological and general physical progress. Particular inquiry was made of subsequent difficulties in feeding or abnormalities of cry or respiration and no such disabilities have been noted by the infant's alert parents. General somatic and neurological evaluations at 5 and at 13 months of age demonstrated no significant abnormalities. Electroencephalogram at 13 months of age was essentially normal.

Discussion

Among the most interesting seizure manifestations in the pharynx-larynx area are those which are associated with organized movements. These performances are sufficiently distinctive to have provoked speculation by J. Hughlings Jackson:

> We must note in slight fits movements of chewing or tasting, swallowing, and writhing movements of the arms during arrest of respiration. I do not believe that these movements result directly from the epileptic discharge, holding that *such* a discharge, so far as it spreads, puts an end to all movements properly so called, "runs them up" into convulsion. . . . I suggest that . . . [these] are the indirect [reflex] results of epileptic discharge of sensory elements. . . . It is exceedingly important to distinguish movements proper from convulsion, which is a contention of many movements . . . (6).

The licking, chewing or swallowing motions which are a familiar part of psychomotor seizures originating in the temporal lobe are examples of organized motions which are remotely instigated and, thus, are of secondary or indirect relation to seizures, as Jackson would distinguish them.

The most common motor expression of seizures originating in the mid-brain or medulla are those of simple sustained or intermittent occlusion of pharynx and/or larynx. Less frequently, the pattern of manifestation is that of simultaneous myoclonus in various but individually consistent muscle distributions within this region (7–9). A similar variant is that which accomplishes paroxysmal hiccup. Repetitive or "paroxysmal" sustaining efforts of cough are also attributed to seizures of medullary origin (10).

In the clinical example reported herewith, we infer that the repetitive gulping or glossopharyngeal respirations are an integral part of seizures of medullary

origin. This is indicated by the sequence in which the sustained tonic occlusion or closure of the pharynx and larynx shifts abruptly to the organized rhythmic sequential performance of GPR. A question might be raised whether this may be a manifestation of clonus following the tonic seizure of the pharynx region; this possibility seems to be excluded by the duration and the organized, progressive pattern of these motions.

The interrelation of the glossopharyngeal breathing as observed in this infant with other elements of this infant's seizure episodes are of interest. During the maximal manifestation of seizure, as these were observed clinically without radiologic assistance, the upper respiratory way was occluded completely and prolongedly, and forcible thoracic efforts of respiration were futile. As the seizures were moderated by large amounts of anticonvulsant medication, the tonic phase of respiratory occlusion was abbreviated and succeeded immediately by the repetitive glossopharyngeal performances. In this lesser state of seizure, the infant was not cyanotic, or would become only minimally so, and there would be little elevation of pulse rate; each of these criteria was in contrast to the dramatic degree of hypoxia that the subject had demonstrated in her earlier and more severe seizure manifestation. It would seem apparent, therefore, that hypoxia is not a mechanism of elicitation of this GPR phenomenon, for why, then, was it not demonstrated at the end of the more severe seizure episodes, when the subject was deeply prostrated, limp, and demonstrated only minimal phrenic respiration?

It is of interest in this connection to compare GPR with the abnormal "snapping" respiration (*Schnappatmung*) observed by Peiper (11), Schmidt (12), and Ahlfeld (13) in the natal moment or late in the apneic spells of immature infants. These snapping respirations are clearly different from the glossopharyngeal respirations that we have noted in the above patient, for in this patient there was essentially no motion of opening or closing of the mouth, but rather this was entirely a phenomenon of the pharyngeal region, including the posterior portion of the tongue. Peiper (14) suggests that the snapping type of respiration reflects hypoxia, an impression which was well-supported by animal experimentation of Peiper and Cammann (15) in which animals were rendered hypoxia.

In interpretation of GPR in this infant, we are left with the possibility of an exceptional mechanism of elicitation of this rare phenomenon incident to this subject's seizure, or with the possibility that the normal performances of the pharynx were temporarily inhibited or otherwise impaired as a part of the seizure circumstance and that this more primitive mechanism of GPR was thus "uncovered" and allowed to perform without the normally dominant performances or actions. This "uncovering" of more primitive or elementary mechanisms is a familiar effect of seizure, as illustrated by the temporary appearance of the extensor pattern plantar reflexes in some epileptic subjects during the postictal disability of a grand mal tonic-clonic convulsion.

It should be mentioned again, however, that all normal medullary governed performances are not inhibited or incapacitated at this time, for phrenic respiration does

continue, though it is apparently futile as the pharynx and larynx are not an open channel during repetitive GPR but apparently are reciprocally valved at the upper pharynx or at the larynx at all times. In possible further extension, we suggest that, in this circumstance, glossopharyngeal respiration is not alternative to normal phrenic respiration but is possibly alternative to other mature functions, such as deglutition.

The relatively slow periodicity of these GPR motions, their stable cephalo-caudad sequence, and their apparent physiologic utilization indicate that these brain stem governed performances are not distorted by the mass random effects of seizure. Their periodicity is comparable to that described in the GPR performance elicited voluntarily in respiratory-impaired poliomyelitis patients.

The particular neuropathologic lesions effecting paroxysmal phenomena in the pharynx region of infants and children has received comparatively little comment in the literature, for the great majority of these lesions and their associated disabilities are benign and do not afford necropsy opportunity. Thus, the infants described by Allen *et al.* (16), having laryngeal occlusion, recovered completely and the same good prognosis is reported for infants having "laryngismus stridulus" and a variety of temper tantrums with breath-holding spells (10). Referring to the latter, Peiper (11) confidently affirms that "passing out" is completely harmless. Likewise, Kanner (17) and Low (18) point to the good prognosis of the infants and small children having temper tantra and breath-holding spells.

In this infant the situation was apparently benign, as indicated by the diminishing requirements of anticonvulsant medication for adequate seizure control, the good general performance of mouth, pharynx, and larynx in feeding and in cry, as judged by cinefluorography, and her good general neurological development in the succeeding 12 months.

This phenomenon is probably less rare than this isolated observation suggests. Physicians oriented to this possibility will probably detect it in other infants having seizures principally and entirely restricted to pharynx and larynx region, particularly if observation is supplemented with stethoscopic auscultation in the area of the larynx. Unfortunately, electroencephalography may be of comparatively little value in detection of these focal brain stem seizures, for paroxysmal activity originating in these sites may not be reflected in the electroencephalograms obtained in usual manner from scalp leads.

Summary

The rare and distinctive motor performance of glossopharyngeal respiration (GPR) is reported as a part of seizure manifestation in an infant one month of age. This GPR is essentially identical with that learned spontaneously or by intention in some poliomyelitis patients having severe respiratory paralysis. It has also been observed as an isolated performance in the respiratory transition at the moment of birth. It is inferred that this is a mechanism or performance which a subject has potentially but does not otherwise employ.

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Disability of Oral Function in an Infant Associated with Displacement of the Tongue

Therapy by Feeding in Prone Position

by YASUAKI TAKAGI[1] and JAMES F. BOSMA[2]

Introduction

Published reports of disability of oral and pharyngeal function associated with retrusion of the mandible have been concerned generally with static criteria of observation; such as the deficient mobility or the hypoplasia of the mandible (1–3), displacement or hypoplasia of the tongue (4), or cleft or hypoplasia of the palate. The disabilities associated with these anomalies or displacements have been notably variant in the individual infants. Robin (5), Eley and Farber (6), Pruzansky and Richmond (7), and Beers and Pruzansky (8) describe rapid general improvement in oral function in the first postnatal weeks, so that ventral displacement of the tongue, by support devices (6, 9, 10), by other position-facilitating devices, such as the bottle guard of Davis and Dunn (11), or by plastic surgery (12) is needed only as a temporary expedient. Abrupt improvement in function, including relief of symptoms of upper respiratory obstruction, has resulted from assumption of prone or partially upright ("orthostatic") position (5).

In the subject of this report, the palate and tongue were each of normal size, contour and motion, but the tongue was caudally displaced, the mandible retruded, and the tongue and the hyoid insufficiently supported from the mandible. Swallow was adequate in a variety of head-neck positions, but performance of suckle was accomplished adequately only when the infant was in extension at the neck, usually in prone position. When in supine position the tongue commonly intruded into the pharynx during attempted suckle and the palate-tongue barrier between mouth and pharynx was interrupted. With institution of prone feeding, employing a novel apparatus, and general maintenance of prone position, the infant abruptly acquired adequate capacity for feeding and recovered rapidly from severe malnutrition and from recurrent bronchopulmonary aspiration.

Subject and Observations

The subject of this report was a male infant, born at weight of 2635 gm, of spontaneous labor, completing pregnancy of uncertain duration. The mother was 14 years

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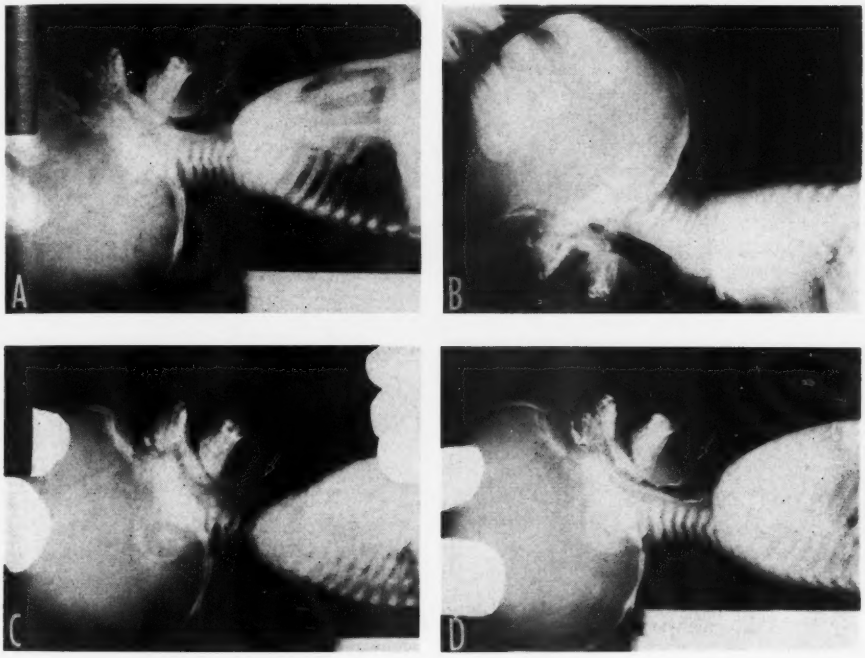

Fig. 1. Lateral radiographs of subject at standard alignment, focal film and subject-film distances. Traces of Lipiodol® in nose and mouth. *A*. Initial radiograph in supine position at 16 weeks. Demonstrates retrusion of mandible, which is of grossly normal size and contour and has normal dental development. Palate is of normal contour and position, with epipharynx patent. Tongue is of normal size, but displaced caudally, along with hyoid (at arrow). *B*. Prone position, in active opisthotonus, on same day as Fig. 1*A*. Note increase in anteroposterior diameter of the pharynx. *C*. Infant in supine position, after 13 days of prone feeding and generally prone position. The mandible was displaced ventrally 4 mm (film measurement) in relation to basiocciput and C–1, compared with A. The tongue is in more ventro-cephalic position within mouth. The hyoid is unchanged in relation to cranium and odontoid process. *D*. Infant in supine position, after an additional 14 days in prone position. The mandible, tongue, and hyoid are essentially unchanged, compared with Figure C.

of age, of Spanish ancestry, and was essentially well at time of delivery except for a mild respiratory infection. There was no information of like or possibly related abnormality in maternal ancestry. The father was unknown.

From birth until initial observation in this Department, at 16 weeks of age, the infant had severe disability of feeding and of respiration, for which problems he had been retained in a local hospital. The extent of these difficulties was indicated by severe malnutrition (weight at this time was 3600 g; height 47 cm), and by auscultatory and roentgen evidence of chronic diffuse bronchopulmonary disease, identified radiographically as "aspiration pneumonia".

The infant demonstrated hypodevelopment of the frontal bones, with persistence of the metopic suture and an enlarged anterior fontanelle, 4 × 5 cm in diameter. The face was generally small, with small maxillae and a retruded and apparently small mandible, without lateral asymmetry. The external auditory canals were obstructed bilaterally by the displaced condyles of the

mandible. There was moderate protrusion of the eyes from their shallow orbits. By inspection, the tongue appeared to be small and displaced dorsally within the mouth. The general contour of the anterior or free portion of the tongue was normal at rest and in motion. The hard palate was of contour appropriate to deficiency of moulding by the tongue. The soft palate was normal; the uvula was not bifid. The hypopharynx and larynx appeared normal by satisfactory direct visualization. The ears were normal; the neck was normal by inspection and palpation and the cervical vertebrae were normal radiographically. There was no abnormality of cry and cough, and the pharynx was well cleared of secretions by swallow. An incidental observation was that of greater strength or maturity of the cervical extensor compared with the flexor musculature.

Lateral roentgenograms (Fig. 1) confirmed the visual impression of small size of the frontal cranial bones and the facial skeleton. The angle of the mandible was normal. Radiographic studies gave no evidence of hypoplasia of the unerupted teeth.

The still radiographs demonstrated grossly normal length and diameter of the palate, and films obtained during cry demonstrated normal and symmetrical dorsal angulation of the palate by its levator muscles and symmetrical alignment of the palatopharyngeal folds which rose into prominence with this maneuver. The tongue was also normal in gross mass, demonstrating normal elongation at its tip and achievement of a cup-shaped contour incident to cry. In none of these maneuvers did we see an exaggeration of the vallecula which would be suggestive of hypoplasia of the tongue, or, alternatively, of a disproportion of motor effect of the extrinsic lingual muscles. The epiglottis was of normal length. The hyoid body was displaced caudally and ventrally in relation to the mandible and to the cervical vertebrae.

The infant demonstrated normal hunger and a normal rooting response when touched on the cheek. He attempted avidly to suckle in customary supine bottle-feeding position, but was unable to accomplish firm and sustained enclosure of the nipple or to effectively express milk from it. These disabilities were further demonstrated on lateral cinefluorographic study (Fig. 2), by which the motions of suckle were found to be varied in pattern and irregular in schedule. The mandible was intermittently protruded without a normal rotatory motion. The tongue was intermittently displaced upward and its tip enclosed the end of the nipple. The tongue also intruded intermittently into the pharynx to approximate its dorsal wall, in a manner inappropriate to a normal suckle performance.

Swallowing occurred without discrete accumulation of bolus. These swallows were entirely of normal form, accomplishing complete obliteration of the pharyngeal cavity by approximation of the pharyngeal wall, palate, and tongue. And, at the conclusion of swallow, the pharynx was empty.

During 16 days of hospitalization a variety of feeding methods were employed by well-experienced nurses, and finally, in exigency, gavage feeding was instituted. During this time the infant lost weight, from 3060 to 3033 grams. His respiratory disability continued.

Feeding of the infant in prone position was then attempted on trial basis and, when this manner of feeding was found to be effective, cinefluorographic studies of it were undertaken. It was found that in this position the infant accomplished an enclosure of greater length of the nipple and effective stroking actions of the tongue (Fig. 3). Bolus was accumulated in a pool of appropriate size between the mid-dorsum of the tongue and the hard palate. The mandible was generally in a more ventrad position and its motions were in a pattern more appropriate to normal suckle. These oral adaptations to suckle were accomplished with little or no upward displacement of the hyoid from its abnormal position. The motions of sucking were in normal sequence and rhythm.

To feed the infant in prone position, various patterns of L-shaped tubes were designed and tried. These tubes had a nipple at their shorter end and volume scale on the

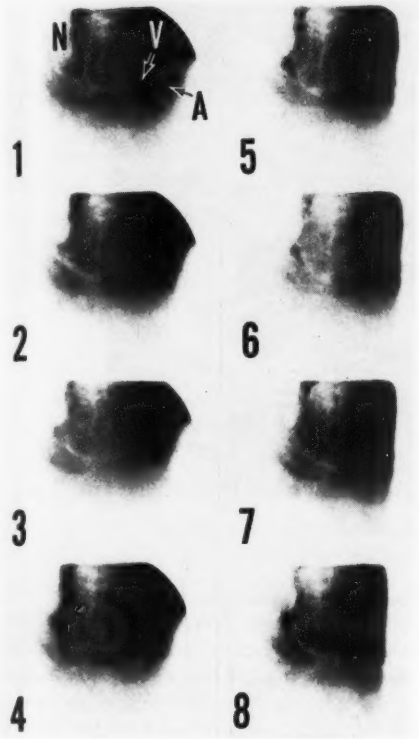

Fig. 2.

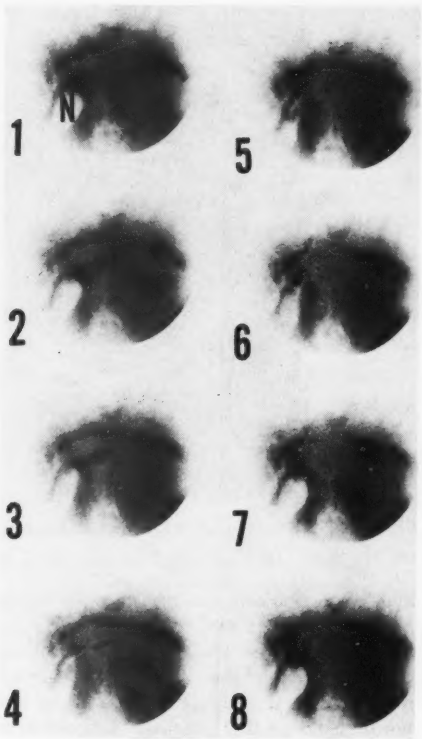

Fig. 3.

Fig. 2. Selected frames of cine film obtained at 32 frames per second, showing distortion of suckle in supine position. Cervical vertebrae are minimally discernible at lower margin of frames. Nipple is indicated in first frame by N; V indicates vallecula, and A indicates arytenoid mass. *1.* Tongue tip apposed to end of nipple. Mesopharynx and epipharynx open. *2.* ($^4/_{32}$ second later.) Tongue tip at end of nipple, tongue displaced dorsocephalically. Epipharynx is closed. *3.* ($^4/_{32}$ second later.) Tongue tip at end of nipple, tongue further displaced dorsocephalically, and epipharynx and portion of mesopharynx are closed. *4.* ($^8/_{32}$ second later.) Tongue tip barely touches end of nipple, tongue withdrawn from palate, but epipharynx still closed. *5.* ($^{16}/_{32}$ sec. later.) Tongue tip touching nipple. Tongue approximates palate. Epipharynx closed. *6.* ($^2/_{32}$ second later.) Further approximation of tongue to nipple and initial compression of nipple. Epipharynx closed. *7.* ($^2/_{32}$ second later.) Tongue compresses end of nipple and generally approximates palate. Epipharynx closed. *8.* ($^3/_{32}$ second later.) Tongue returning caudad. Nipple resumes original contours. Epipharynx closed.

Fig. 3. Consecutive frames of cine film obtained at 32 frames per second, showing suckle in prone position. Study immediately consecutive to that of Fig. 2. Cervical vertebrae are discernible at upper margin of frames. In suckle preparatory position, the tongue continues in normal apposition to palate (as in frame *1*) and to nipple (*N*). The tongue moves progressively in dorsocephalic direction, compressing nipple and further approximating palate. In frame *5*, the tongue and palate beyond nipple are apposed entirely and the palate is displaced into epipharynx. In frames 6–8 the epipharynx is closed discretely at the dorsal protrusion of the palate, and the dorsal portion of the tongue continues its rotation dorsocaudally, remaining in apposition to the nipple but without compressing it.

Fig. 4. Feeding in prone position, using novel feeding tube.

longer end. Variable pressures of milk in the nipple could be arranged by regulating the amount of milk in the longer portion of the tube. Feeding in this position was further facilitated by thickening the formula by rice powder, though this supplementation was of little aid in attempted feeding of the infant in supine position.

After 13 days of prone position feeding and general maintenance of this position, a repeat roentgenogram was obtained at rest (Fig. 1 *C*) which demonstrated a ventrad displacement of the mandible toward a more normal position and the tongue generally higher and in more normal relation to the hard and the soft palate. Brief comparison observation in lateral recumbent position demonstrated that suckle could also be accomplished adequately if the infant's head and neck were extended. Fig. 4 illustrates the specially designed feeding tube, with the infant in prone position.

The infant was fed adequately in prone position, gained weight well (from 3033 g to 3373 g in 13 days), and demonstrated feeding satisfaction. In the next 2 weeks of observation, his mandible assumed normal position, recovering from its retrusion (Fig. 1 *D*). The infant slowly acquired capacity for adequate suckle in any position. The auditory canals became consistently patent. With recovery from malnutrition, he became increasingly vigorous and normally responsive and discriminatory. Evidences of broncho-pulmonary aspiration diminished progressively. There were no evidences of continued coordinative disability or reflex abnormality of the trunk or limbs.

Discussion

The abruptness and change in quality of this infant's suckle performance with initiation of prone position feeding were remarkable. The nature and extent of this change could be defined by cinefluorography. By this means, it was shown that the tongue achieved more normal position in relation to the nipple and to the hard and soft palate. But the most significant change was that of acquisition of normal patterns of motion of tongue and mandible

and their arrangement into the continued rhythmic performance that characterizes normal suckle feeding. An appropriate effect of this normal suckle action was the progressive achievement of more normally sustained position of these mobile elements of tongue and mandible in intervals between suckle feeding.

In consideration of abnormalities of performance in subjects having anomaly or neurological impairment in the oral-pharyngeal region, it has been customary to ascribe the disability to observed distortions of size, form or spatial relations. By this reasoning, it would have been inferred from the initial radiologic studies of this infant that impairment of his oral function was due to caudal displacement of the tongue, along with the hyoid and larynx, and to dorsal displacement or retrusion of the mandible. But we noted that the infant was comfortable in prone position, and that he suckled optimally in slight cervical opisthotonus, in which circumstance the distance from basicranium or maxilla to sternum was increased. And the tongue was actually drawn farther away from the caudally displaced hyoid to accomplish its approximation to nipple and palate in this improved performance (see Fig. 1). It was apparent, therefore, that this improvement in oral function reflected better coordinated actions of the musculature of tongue and mandible.

The critical element accomplishing improvement in quality of suckle and other oral performance was not the infant's orientation in space—whether he was prone or supine—but was his position of cervical extension, as was demonstrable by observation that he suckled adequately when lying on his side, provided he was actively assuming an extension position at neck.

This facilitation of suckle performance by head and neck extension is not readily explained. The interaction of oral and pharyngeal mechanisms with cervical posture is familiar. Thus, extension at the neck occurs involuntarily as a facilitation of dyspnea or of loud speech, song or shout. Subjects having paralytic dysphagia employ an individualized variety of habitual head-neck maneuvers to facilitate swallow, the most common of which is symmetrical or asymmetrical extension of head and neck (13). Recently, in more particular radiologic observation of position of structures in the oral and pharyngeal region at times of active and passive displacement at head and at neck, it has been observed that extension at the neck is consistently associated with opening of the airway by ventral displacements of the structures of the ventral pharyngeal wall, by which maneuver the anteroposterior diameter of the pharynx is increased, despite protrusion of the flexed cervical spine (14). This interaction of function in the oral and pharyngeal regions with cervical posture is more apparent in the young infant. Thus, the infant during cry consistently extends at head and neck and also assumes a median alignment of head, neck, and trunk. Opening of the pharyngeal airway has also been noted in association with cervical extension in infants (compare Figs. 1 *A* and 1 *B*).

For infants having clinically similar impairments of oral and pharyngeal function, though without associated cleft of the palate, Robin had recommended prone feeding at breast. This procedure of suckle feeding in prone position probably is

analogous in its therapeutic mechanism to feeding in upright or "orthostatic" position as recommended by Robin (5) for slightly older infants having disability of suckle feeding. We are reminded that the infant who has marginal achievement of upright posture at head, neck, and upper trunk accomplishes this upright posture in a position of cervical extension. And, furthermore, if Robin's infant subjects had the disproportionate maturation of the dorsal and extensor cervical musculature which was demonstrated in our subject, his subjects would the more probably be in cervical extension in their "orthostatic" position.

In the infant whom we have described, having hypoplasia of the face and of the musculature accomplishing normal spatial arrangement of the mandible and hyoid, the displaced oral structures performed poorly, but this disability was not primarily because of their caudal displacement. A theoretical explanation is that this infant's effortful extension at neck occasioned a reciprocal inhibition of the postural efforts of the musculature of mandible and hyoid, so that his musculature might be freely utilized in suckle. And, in this neurophysiological circumstance, a normal central regulation of suckle occurred, so that this action became more rhythmic, rapid, and effective. These explanations seemingly fit all of the information which we have accumulated in observing this infant by cinefluorography and also by our gross clinical experience with him. But these explanations remain theoretical, as the particular neurophysiological mechanisms of interaction of these oral and pharyngeal performances with cervical posture are undefined.

The mechanism of displacement of he mandible from its retruded position is likewise obscure. That this retrusion was pathological in degree in this subject was indicated by the compression of the external auditory canals by the mandibular condyles. The mandible progressively assumed its more normal anteroposterior rest position, in relation to maxillary skeleton, after suckle function had improved. Robin (5) had also observed the progressive ventrad displacement of the mandible in infants subjected to orthostatic feeding.

These observations of abrupt improvement in pattern and effectiveness of oral function with change in cervical posture, accomplished without significant correction of the caudad displacement of the hyoid or of the dorsad displacement of the mandible would lead us to suggest the progressive change in oral-pharyngeal function of these infants which occurs in the first postnatal weeks may be related to neurological development of their branchial and cervical postural mechanisms and of the interaction of these mechanisms. This suggestion gains support from the difference in reported schedule of improvement in the oral function compared with the differential growth of the mandible and the tongue, for this schedule of improvement in function is certainly more rapid than the disproportionate growth of mandible and tongue, by which ventrad displacement of the retruded tongue is supposedly accomplished.

The role of abnormality of coordination of oral function in these subjects having hypoplasia or dysplasia in the oropharyngeal region requires further elucidation. Another consideration is the possibility

that the apparent dysplasia may itself be a reflection of a coordinative disturbance.

Search for a coordinative disturbance which is of primary or associated etiology in such infants would probably be most profitable if restricted to those infants having no gross anomalies, such as the commonly associated cleft of the palate (5–7).

Summary

This is a report of an infant who had disability of feeding and other oral function similar to that observed in those having hypoplasia fo the tongue and/or palate. But in this subject these structures were of normal size, form, and motion. It was inferred that disability in this subject was due to inhibition of these oral performances incident to abnormalities of cervical postural mechanism.

It is proposed that normal suckle can be performed only against a background of regional inhibition of the musculature accomplishing anteflexion of head and neck.

The particular clinical problems of this infant were relieved by a novel technique of prone position feeding.

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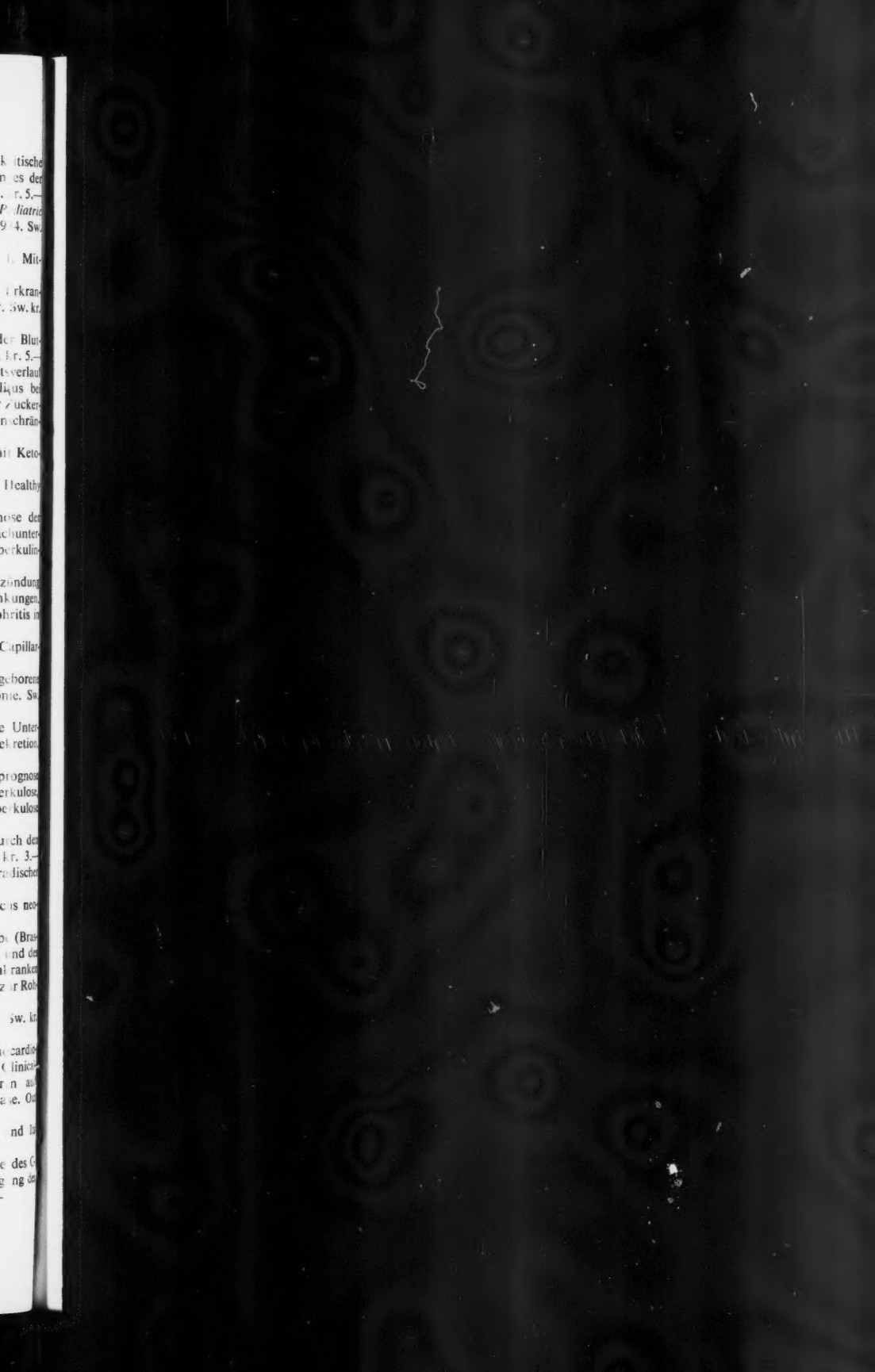

FROM THE INSTITUTE OF MEDICAL CHEMISTRY, UNIVERSITY OF UPPSALA AND FROM THE PEDIATRIC CLINIC, UNIVERSITY HOSPITAL, UPPSALA, SWEDEN.

FREE ERYTHROCYTE COPRO- AND PROTOPORPHYRIN

A METHODOLOGICAL AND CLINICAL STUDY

BY

LARS WRANNE

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Introduction

The presence of free porphyrin in the erythrocytes was first established by van den Bergh and Hyman (1928) and the porphyrin was later on identified as protoporphyrin IX by Grotepass (1937), i.e. the same porphyrin as that present in hemoglobin. Watson (1950) reported that the free erythrocyte protoporphyrin was accompanied by small amounts of another porphyrin. This was shortly afterwards isolated and identified as coproporphyrin (Schwartz and Wikoff 1952). Using a recently developed semi-quantitative microchromatographic method, Sturgeon, Chen and Bergren (1958) demonstrated the presence of free uroporphyrin in erythrocytes of normal individuals.

The significance of the free erythrocyte protoporphyrin has been discussed greatly during the years since its discovery. Two of the main factors which appear to influence the amount of protoporphyrin are (1) increased erythropoiesis and (2) factors interfering with the utilization of iron in the synthesis of hemoglobin, and iron deficiency. Both these factors have been found to increase the free erythrocyte protoporphyrin. Watson (1950), studying the free erythrocyte coproporphyrin, found that the concentration of this pigment was closely correlated to the reticulocyte count and considered it to be "a chemical index" of the intensity of blood formation. Finally, Sturgeon, Chen and Bergren (1958), in their investigations of free erythrocyte uroporphyrin, found that this pigment was also correlated to the rate of the blood formation since increased amounts occurred in hemolytic anemias.

The present investigation was started in 1956 to study the physiological behaviour of free erythrocyte copro- and protoporphyrin in healthy infants and children and in patients with various hypochromic anemias. A family investigation prompted by a case of hypochromic anemia with disturbed heme-metabolism has been published elsewhere (Wranne 1959). In 1956, uroporphyrin was not known to be a normal constituent of erythrocytes and thus was not separately searched for. Since earlier methods for the analysis of free erythrocyte porphyrins were found insufficient, it proved necessary to devote the major part of the work to methodological studies. Associated problems, such as the nature of the porphyrins and the porphyrin content of plasma, were also studied. Finally, the effect on the free porphyrins of a sudden change from iron deficiency to a state of sufficient iron supply was studied after starting intravenous iron therapy.

PART ONE

Methodological Study

CHAPTER I

Earlier and present methods

1. Short review on earlier methods of determining free copro- and protoporphyrin in erythrocytes

Extraction and purification of protoporphyrin. Since the first description of free red-cell protoporphyrin by van den Bergh and Hyman (1928), at least seven methods for the quantitative determination of protoporphyrin in erythrocytes have been published. The first, proposed by van den Bergh, Grotepass and Revers (1932), comprised extraction from the red cells with a mixture of ethyl acetate and glacial acetic acid for two hours. After being washed with water, this extract was extracted with 5 % HCl. After one purification:

$$\text{HCl} \xrightarrow{\text{Neutralization}} \text{Ether} \xrightarrow{\text{H}_2\text{O wash}} 5\ \%\ \text{HCl}$$

the protoporphyrin was finally estimated by its fluorescence in ultraviolet.

Several modifications of this procedure have been published; the alterations chiefly concern the time of extraction of the erythrocytes, the concentrations of the hydrochloric acid and the methods for the final estimation of the porphyrin. However, the principles of van den Bergh and coworkers have been essentially unchanged. In Table 1, the different modifications are briefly presented. Most of these modifications include erythrocyte coproporphyrin as well as protoporphyrin, hence the term "erythrocyte porphyrin" would be more appropriate. However, the main part generally consists of protoporphyrin.

The great number of modifications indicates that the ideal conditions for the analysis have been difficult to find. The problems inherent in the estimations of these small quantities of protoporphyrin are chiefly dependent on its instability in strongly acid solutions and when exposed to light. In order to obtain a favorable distribution of the porphyrin between organic solvent and hydrochloric acid, and in order to get reasonable concentrations of porphyrin in the final extracts, a strong mineral acid is necessary. Schumm (1939) and Grinstein and Wintrobe (1948) used 25 % HCl. However, in strong acid solutions, the vinyl side chains of protoporphyrin are readily changed to hydroxyethyl with formation of hematoporphyrin. Other changes may occur as well (Schumm 1927, Paul 1953). The formation of hematoporphyrin is of little significance when only protoporphyrin is estimated; if coproporphyrin is also determined, serious errors may be introduced.

Protoporphyrin is rapidly destroyed when exposed to ultraviolet light (Lageder 1936, Grinstein and Watson 1943). Diffuse

TABLE 1. *Methods for the quantitative determination of free erythrocyte porphyrins.*

	v. d. Bergh, Grotepass and Revers 1932	Schumm 1939	Grinstein and Watson 1943	Grinstein and Wintrobe 1948	Schwartz and Wikoff 1952		Present method	
Volume of erythrocytes	10–20 ml	40 ml	5 ml	1 ml	5 ml		2–4 ml	
First extraction and subsequent washings of the precipitate	EtAc/HAc 3/1 100–150 ml 2 hours	EtAc/HAc 3/1 300 ml 30 min. + 100 ml × 3	EtAc/HAc 3/1 50 ml 2 min. + 15 ml × 3	EtAc/HAc 3/1 10 ml 2 min. + 5 ml × 3	EtAc/HAc 4/1 50 ml several times until colorless extract		EtAc/HAc 4/1 40 ml 2 min. + 10 ml × 3	
Washing	H_2O 3–4 times	H_2O 300 ml × 4	H_2O 3 times	H_2O 7–8 ml × 3	3% NaAc 40–50 ml × 3		3% NaAc 15 ml × 3	
First extraction with acid	5% HCl	25% HCl 2 ml × 7–10	10% HCl 2 ml	10% HCl 2 ml	3 *N* HCl 5–10 ml		5 *N* HCl 4 ml × 4	
			until absence of fluorescence in extract					
Neutralization and additions	NaAc		NaAc + 1 ml glac. HAc	NaAc + 1 ml glac. HAc	NaAc		NaAc	
Second extraction by organic solvent	Ether	Chloroform (evaporation, dissolution in HCl)	Ether equal volumes × 3	Ether 10 ml × 2	Ethyl acetate 50–75 ml × 3		Ethyl acetate 50 ml × 3	
Washing			1% Na_2CO_3, few ml + H_2O × 2	1% Na_2CO_3 2 ml × 1 + H_2O 2 ml × 2	H_2O × 1		H_2O 3 ml × 2	
Second extraction with acid	5% HCl		5% HCl 1.5 ml × 3–4	25% HCl 1.5 + 0.3 ml	*First* 0.1 *N* HCl 3–5 ml "exhaustively". Combined extracts washed with $CHCl_3$ 5 ml × 2, washes added to EtAc	*Second* 3 *N* HCl "exhaustively"	*First* 0.24 *N* HCl 4 ml × 6 Extracts not pooled	*Second* 5 *N* HCl 4 ml × 4 Extracts pooled
Physical estimation in final extracts	Fluorometry	Spectrophotometry (photographical method)	Evelyn colorimeter	Beckman DU 409 mμ	Fluorometry	Evelyn colorimeter	Separate readings of fluorescence in each extract	Spectrophotometry at Soret peak, 380 and 430 mμ
Porphyrins probably present in final extracts	Protoporphyrin + coproporphyrin	Protoporphyrin	Protoporphyrin + coproporphyrin	Protoporphyrin + coproporphyrin	Coproporphyrin	Protoporphyrin	Coproporphyrin (+ traces of protoporphyrin)	Protoporphyrin

daylight is also deleterious. Consequently, the protoporphyrin analysis should be performed quickly and as far as possible in the dark. However, high efficiency in extracting requires perfect separation of the phases. This calls for good light and is time-consuming and therefore increases the risk for protoporphyrin loss.

Methods for the physical estimation of protoporphyrin in the final extracts. Van den Bergh and coworkers (1932), Angeleri and Vigliani (1935), Lageder (1936) and Ward and Mason (1950) estimated the protoporphyrin content by its fluorescence in ultraviolet light. Because of the instability of protoporphyrin when exposed to light, many authors have exchanged the fluorometric analysis for estimations of the light absorption. Seggel (1940) measured the absorption in the visible part of the spectrum, while Schumm (1939) determined the light absorption in the Soret band (near ultraviolet) by the photographic method. The use of a photoelectric colorimeter, which Grinstein and Watson (1943) introduced in this field made the study of the Soret band much easier. Even better measurements could be achieved by a photoelectrical spectrophotometer. This allows a check of the identity of the porphyrin by measuring the wavelength of the maximum of the Soret band.

Extraction and purification of proto- and coproporphyrin. The method described by Grinstein and Watson (1943) was modified by Schwartz and Wikoff (1952) in order to permit the simultaneous analysis of proto- and coproporphyrin. The principles of the modification are shown in Table 1. Since this method will be frequently discussed in the following discussion a short description will be given here.

At least 5 ml of erythrocytes are extracted with a 4:1 mixture of ethyl acetate and glacial acetic acid. The extraction is repeated several times. The combined extracts are washed three times in a separatory funnel with a 2 % aqueous solution of sodium acetate and then extracted exhaustively with 3 *N* HCl. The combined acid extracts are neutralized to Congo red reaction with sodium acetate and the porphyrins transferred to ethyl acetate. The ethyl acetate solution is washed with water and extracted exhaustively with 0.1 *N* HCl. The combined 0.1 *N* HCl extracts are washed with chloroform in order to remove co-extracted traces of protoporphyrin; the washings are added to the ethyl acetate solution. The latter is finally extracted by 3 *N* HCl several times. The porphyrins contents of the 0.1 *N* HCl extracts (coproporphyrin) are determined in a sensitive fluorometer, whereas the protoporphyrin contents of the 3 *N* HCl extracts are measured in an Evelyn colorimeter.

The method just described was used without especial changes in all earlier quantitative investigations of free erythrocyte proto- and coproporphyrin in humans. However, Proel and May (1952) studying scurvy in monkeys, preferred 0.33 *N* HCl to 0.1 *N* for the extraction of coproporphyrin. Since no thorough examination of the efficiency and reliability of the Schwartz and Wikoff method has been published, it was considered necessary for the purpose of the present investigation to submit the method to a closer study. The results obtained convinced the author that the method of Schwartz and Wikoff required modifications in several respects. In the following, the procedure finally adopted is first described. After that, the details of the methodological study are reported.

2. The author's method

The blood sample is centrifuged at 3000 rpm for 30 minutes and the plasma carefully removed. In a separate sample, a hematocrit determination is made. The erythrocytes, 2 to 4 ml, are transferred to a flatbottomed test tube and thoroughly mixed with 40 ml of a 4 : 1 mixture of EtAc[1] and glacial HAc. The precipitate is finely ground with a glass rod for two minutes and placed on a glass filter. The extract is then filtered with gentle suction. The precipitate is washed three times with 10 ml portions of the mixture; the third wash is almost colourless as a rule. The combined EtAc/HAc extracts are washed three times in a separatory funnel with 15 ml of a 3 % aqueous solution of NaAc. The porphyrins are removed from the EtAc/HAc solution by four extractions with 4 ml 5 *N* HCl. The combined HCl extracts are neutralized with NaAc, using Congo red as indicator; then they are extracted three times with 50 ml EtAc. The combined EtAc solutions are washed twice with 3 ml distilled water, the washings being discarded. Sufficient time should be allowed for the separation of the two phases. Finally, the porphyrins are extracted first with 4 ml portions of 0.24 *N* HCl six times, then with 4 ml portions of 5 *N* HCl four times. The coproporphyrin (and traces of the protoporphyrin) goes into the 0.24 *N* HCl extracts, the fluorescence of each being determined by comparison with a coproporphyrin standard. A sensitive fluorometer is required. The sixth extract is considered to be free from coproporphyrin, and its fluorescence is used as blank. After correction for this blank, the coproporphyrin content in the preceding five extracts is calculated. The protoporphyrin content is determined spectrophotometrically in the pooled 5 *N* HCl extracts. The value is corrected according to the principles of Rimington and Sveinssen (1950) using the coefficient given by With (1955). 5 cm cells are used. The method can also be applied to the determination of porphyrin in 5 ml of plasma.

Recovery experiments, described in Chapter V, revealed that the average recovery of added protoporphyrin was about 80 % and that of coproporphyrin about 75 %. The results were therefore corrected by multiplying with the factors 1.25 (protoporphyrin) and 1.33 (coproporphyrin).

3. Reference substances

Protoporphyrin. Protoporphyrin IX dimethyl ester was prepared according to the method of Grinstein (1947). The preparation was performed on blood from adults as well as on blood from newborn babies. The ester was crystallized from methanol and stored in dry state in the dark. Before use, the ester was hydrolyzed at room temperature overnight by 7 *N* HCl. Since protoporphyrin is not stable in strongly acid solution, water was subsequently added to a final acid concentration of 1 *N*. This protoporphyrin was used within a few days. When it was considered important to get protoporphyrin free from hematoporphyrin and other porphyrins with low HCl-numbers, the protoporphyrin was purified according to the principles of Paul (1953). The protoporphyrin is probably also contaminated by other

[1] EtAc: Ethyl acetate, Merck DAB 6, with a trace of EDTA added. HAc: glacial acetic acid, p.a. NaAc: Sodium acetate, p.a.

degradation products. Since the protoporphyrin was chiefly used for recovery experiments these products were thought to be insignificant. Chromatography as described by Eriksen (1953) gave single spots with R_f values between 0.80–0.83. No differences between protoporphyrin prepared from adult blood and cord blood was found.

Coproporphyrin. Coproporphyrin I and III tetramethyl esters were obtained through the courtesy of dr. med. T. K. With, Svendborg, Denmark. The amounts available were very small and then only some tenths of a milligram were hydrolyzed each time. After hydrolysis for 36 hours in 7 *N* HCl, the solutions were diluted to a final acid concentration of 0.2 *N*. When stored in the dark and in highly diluted solution, coproporphyrin was found to be very stable. This has also been noted by Jope and O'Brien (1945). Chromatography according to Eriksen (1958) revealed single spots when coproporphyrin III was applied ($R_f = 0.54$–0.55), but when coproporphyrin I was chromatographed, a double spot was noted, one intense spot with R_f 0.41, another faint spot with R_f 0.53. It seems possible that the I isomer was slightly contaminated by the III isomer, but the presence of another porphyrin cannot be excluded.—The R_f-values found by the present author differ from those found by Eriksen. However, it was noticed that slight differences in the solvents and in the temperature altered the R_f-value considerably. The necessity of using reference substances when chromatographing porphyrins is thus obvious.

No attempt has been made to calculate the specific extinction coefficients of proto- and coproporphyrin. As With (1959) has pointed out, it must be considered safer to use coefficients calculated by investigators who have prepared the substances themselves and have a great experience of their purification. Therefore the coefficients given by Rimington and Sveinssen (1950) as modified by With (1955) have been used. However, the coefficient for coproporphyrin given by With only applies to coproporphyrin dissolved in 0.1 *N* HCl and since the standard solutions for the fluorometric analyses performed during this investigation contained 0.2 *N* HCl, the coefficient had to be recalculated. By comparing coproporphyrin solutions of the same concentrations in 0.1 and 0.2 *N* HCl, With's coefficient 0.817 rose to 0.90. It was found that the presence of ethyl acetate dissolved in the 0.24 *N* HCl extracts increased the fluorescence by about 12 %. To correct this, the coproporphyrin standard solutions, in which no ethyl acetate was present, were made 12 % more concentrated than designated.

During the fluorometric estimation, the standard coproporphyrin solutions were repeatedly exposed to strong ultraviolet light. Nevertheless, no deterioration was noticed during one day's use, and fresh solutions were used every day.

CHAPTER II

Spectrophotometric and fluorometric determination of copro- and protoporphyrin

1. Spectrophotometric determination

The quantitative determination of proto- and coproporphyrin is carried out conveniently by measurements of the light absorption. Porphyrins dissolved in mineral acids show two bands in the visible and one band in the near ultraviolet region. The latter band is very sharp and distinct and suitable for spectrophotometrical analysis. The position of the band is somewhat dependent on the concentration of the acid solvent; in coproporphyrin, the extinction coefficient shows a similar dependency (Table 2).

Grinstein and Wintrobe (1948) introduced the photoelectrical spectrophotometer in order to determine the porphyrin in the final extracts by measuring the maximal extinction in the Soret band. This method has later been used by many other workers. However, as will be demonstrated below, the estimation of a porphyrin by a single measuring of the maximal extinction is seriously disturbed by even small amounts of impurities absorbing in the near ultraviolet region.

Rimington and Sveinssen (1950) have proposed a method for porphyrin analysis in impure solutions. The method is based on the assumption that the light absorption caused by impurities is constant in the region of the Soret band or at least evenly increasing or decreasing. The extinction maximum (E_{max}) and the extinction at 430 and 380 mμ (E_{430}, E_{380}) are measured and the porphyrin concentration is then calculated by aid of a special equation. This method was originally designed for the determination of uroporphyrin in urine but has been found useful for other purposes as well. With (1955) has discussed its application on proto- and coproporphyrin solutions and proposed the following equations:

Protoporphyrin concentration: (μg/ml, in 3 N HCl) = $1.225 \times (2\ E_{max} - E_{380} - E_{430})$
Coproporphyrin concentration: (μg/ml, in 0.1 N HCl) = $0.817 \times (2\ E_{max} - E_{380} - E_{430})$

Since the hematin absorbs light intensely in the 400 mμ-region, the method given by Rimington and Sveinssen could be expected to give better results than a single measurement of the absorption at the Soret peak. In order to study the advantages obtainable by this method, the following experiment was carried out. Erythrocytes were extracted by an ethyl acetate/acetic acid mixture as usual. The washed extract was repeatedly extracted by 5 N HCl to remove all traces of proto- and coproporphyrin. The deep-coloured residue was added to ethyl acetate, in

TABLE 2. *Absorption maxima in near ultra violet and molar extinction coefficients of some porphyrins.*[1]

	Solvent		
	25% HCl	5% HCl	0.3% HCl
Protoporphyrin	411 mμ ε = 278,000	407 mμ	
Coproporphyrin	406 mμ ε = 437,000	402 mμ	401 mμ ε = 531,000
Hematoporphyrin	407 mμ	403 mμ	

(1) Data from Schumm (1939), Grinstein and Wintrobe (1948) and Jope and O'Brien (1945).

which known amounts of protoporphyrin had been dissolved. The volume of the added matter was 1 : 5 and 1 : 50 of the ethyl acetate volume. The protoporphyrin was extracted by 5 *N* HCl, care being taken to obtain perfect separation between the two phases. The HCl extracts appeared quite clear. Two extractions were carried out; and in the combined extracts, the light absorptions at the Soret band peak, at 430 and at 380 mμ were measured. The protoporphyrin content was calculated from the maximal absorption, using the coefficient given by Grinstein and Wintrobe (1948); it was also calculated from the three readings using the method of Rimington and Sveinssen (1950) as modified by With (1955). The results are found in Table 3 and Fig. 1. In

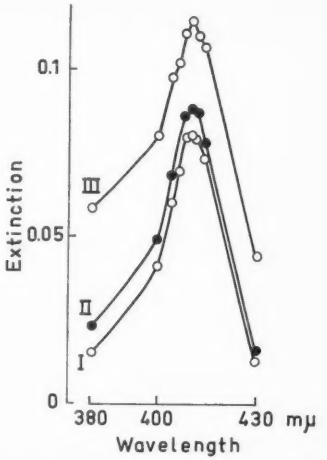

Fig. 1. Influence of impurities on the near ultraviolet spectrum of protoporphyrin solutions. I, II and III refer to the numbers in Table 3.

other experiments, the results of complete analyses of free proto- and coproporphyrin using the Rimington–Sveinssen (1950) correction were compared to the results obtained with a single measuring of the maximal extinction. The analyses were carried out on pure samples of protoporphyrin as well as on samples of erythrocytes. The results are found in Table 4.

Discussion

In the routine analysis of free erythrocyte proto- and coproporphyrin, slight contamination of the final HCl extracts

TABLE 3. *Influence of impurities on the estimation of protoporphyrin in HCl-extracts.*

	Addition of impurity to ethyl acetate	Addition of protoporphyrin μg	Recovery of protoporphyrin μg calculated according to	
			Grinstein & Wintrobe	Rimington & Sveinssen
I	none	1.96	1.80	1.79
II	1:50	1.96	1.98	1.86
III	1:5	1.96	2.59	1.74

TABLE 4. *Complete analysis of free erythrocyte protoporphyrin, results calculated acc. to Grinstein and Wintrobe (1948) and Rimington and Sveinssen (1950).*

Test sample	Protoporphyrin in micrograms, calculated according to	
	Grinstein & Wintrobe	Rimington & Sveinssen
Protoporphyrin, 0.4 μg	0.36	0.28
Protoporphyrin, 0.8 μg	0.54	0.61
Protoporphyrin, 1.2 μg	0.93	0.92
Erythrocytes	0.87	0.39
Erythrocytes	0.74	0.37

by hematin is difficult to avoid despite very careful separation of the ethyl acetate and the HCl phases. The contamination increases light absorption in the near ultraviolet region. If protoporphyrin is estimated by the light absorption maximum in the Soret band in the presence of hematin, the results obtained are too high. The findings shown in Table 3 indicate that successful corrections can be made by aid of a correction proposed by Rimington and Sveinssen (1950) comprising spectrophotometrical readings at 380 and 430 mμ as well.

When the complete procedure for the analysis of free erythrocyte proto- and coproporphyrin was carried out on pure protoporphyrin solutions, it was found that, in the absence of hematin, the results of single measurements of the Soret peak are equal to those obtained by the methods of the authors just mentioned. In contrast to these findings (Table 4), analyses of samples of erythrocytes gave widely different results according to the method of calculating the results. The greater values obtained by calculating the protoporphyrin amount from reading at the Soret peak only are thought to depend on hematin contamination. More reliable results were obtained by using the Rimington–Sveinssen correction. Recovery experiments, described later, indicate that this procedure does not give falsely low protoporphyrin values.

Considering the experimental findings now described, the present author chose to use the Rimington and Sveinssen method (1950) as modified by With (1955) for calculating the amounts of protoporphyrin from spectrophotometrical readings. Previously, this method has only been used by Rubino, Pagliardi, Prato and Giangrandi (1958), by Koskelo (1959) and by Prato, Mazza and Fiorina (1959) for the determination of free erythrocyte protoporphyrin.

2. Fluorometric determination

The fluorescence of coproporphyrin has been studied by i.a. Fikentscher (1932), Jope and O'Brien (1945) and Schwartz, Zieve and Watson (1951). The reports of these authors indicated that fluorometric determination was convenient for very dilute coproporphyrin solutions. The intensity of the fluorescence, however, was dependent on a number of factors; e.g. pH, the presence of ethyl acetate, the

wave-length of the exciting light, etc. During the present investigation, it was found necessary to test the influence of these and some other factors.

In fluorescence estimations, it is also important to choose suitable wave-lengths of the exciting and the emitted light in order to obtain maximum sensitivity and minimum disturbance by scattered light. Since recent studies of the porphyrin fluorescence's activation and emission spectra were lacking, the present investigation was first directed to a spectrofluorometric study of proto- and coproporphyrin.

Fluorescence emission and activation spectra

Apparatus. Emission spectra: Zeiss PMQ II spectrophotometer equipped with the fluorescence accessory ZFM 4 was arranged in the following manner. The light from a mercury lamp, filtered to isolate the 404.7 mμ line, excited the fluorescence. The emitted light passed through the monochromator to the photomultiplier. The slit was set to 1.5 mm. Fluorescence intensity, as judged by the galvanometric deflection, was plotted against wavelength.

Activation spectra: Using the same apparatus, the light from a tungsten lamp, passing through the monochromator, was allowed to excite fluorescence in the sample. The emitted light was filtered through Jena OG 1, 2 mm and registered by a photomultiplier. The slit was set to 1 mm. The amplification was maximal.

When discussing the emission and activation spectra, it must be kept in mind that the galvanometric deflection, which is considered to be a measure of the fluorescence intensity, is subject to a number of additional influences. Emission spectra are influenced by the response of the photomultiplier at different wavelengths and in some degree by the dispersion of the monochromator. Activation spectra are also dependent on the spectral energy distribution of the light source. Corrections for these errors were found to be difficult and uncertain, and the results given below are uncorrected and only valid for this type of instrument.

Results

A study of the *emission spectra* of copro- and protoporphyrin, dissolved in 0.2 *N* HCl revealed that the spectra were essentially equal although the fluorescence intensity of protoporphyrin was weaker than that of coproporphyrin. The highest intensity was found at 590 mμ for coproporphyrin and between 590 and 600 mμ for protoporphyrin (Fig. 2).

A study of the *activation spectra* of proto- and coproporphyrin dissolved in 0.2 *N* HCl and 2 *N* HCl showed, that maximum excitation of fluorescence occurred at sharply defined wavelengths. If a more narrow slit had been used, the peaks would probably have been still sharper, but narrower slits produced too little light-emission to allow safe readings on the galvanometer. A comparison between proto- and coproporphyrin could be made (Figs. 3 and 4). Coproporphyrin exhibited maximum fluorescence at a wavelength distinctively different from that of protoporphyrin. The activation spectra of coproporphyrin I and III were found to be identical, and the III isomer was used throughout the investigation. The wavelength for maximum excitation was found to be approximately the same as the light absorption peak under the same conditions.

Factors influencing fluorescence intensity

Apparatus. The Zeiss spectrophotometer with fluorescence attachment was used. The

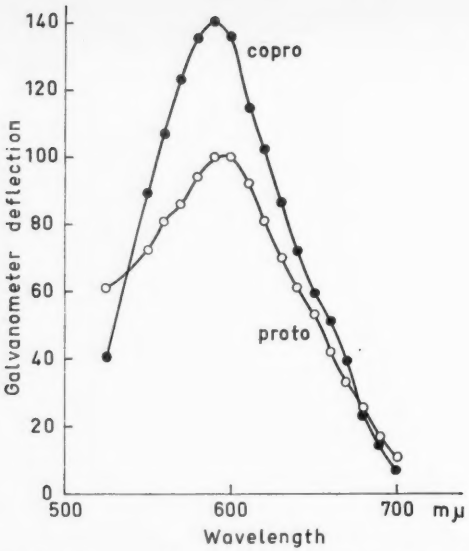

Fig. 2. Emission spectra of coproporphyrin (—●—●—●—) and protoporphyrin (—○—○—○—). 0.2 μg porphyrin/ml. Solvent: 0.2 *N* HCl.

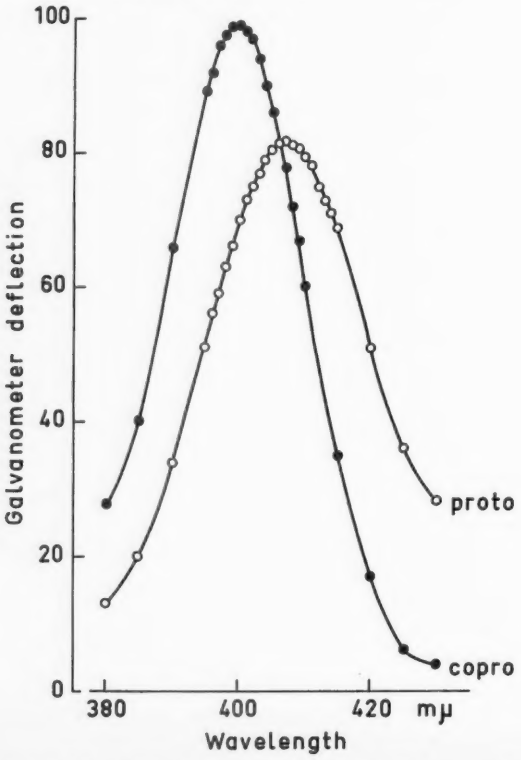

Fig. 3. Activation spectra of protoporphyrin (—○—○—○—) and coproporphyrin (—●—●—●—). 0.160 μg/ml. Solvent: 0.2 *N* HCl.

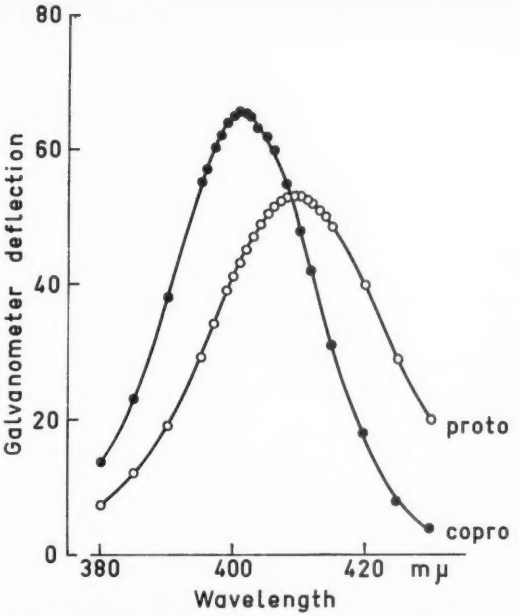

Fig. 4. Activation spectra of protoporphyrin (—○—○—○—) and coproporphyrin (—●—●—●—). 0.160 μg/ml. Solvent: 2 *N* HCl.

404.7 mμ line from a mercury lamp was isolated by aid of the monochromator. The fluorescent light was filtered through Jena filter OG 1, 2 mm, which transmits light of wavelengths above 510 mμ. The intensity of the fluorescence in the samples was compared to that of a coproporphyrin III standard.

Results

Porphyrin concentration. The fluorescence intensity, as judged from the galvanometric deflection, was found to be directly proportional to the concentration of coproporphyrin (Fig. 5). However, when higher concentrations than 0.1 μg coproporphyrin/ml was employed, the fluorescence was quenched.

Hydrochloric acid and sodium chloride concentrations. A standard concentration of coproporphyrin, 0.027 μg/ml was used. Hydrochloric acid and saline were added in varying concentrations. In Fig. 6, the suppression effect of increasing concentration of the acid is illustrated. In Fig. 7, the slightly less pronounced effect of NaCl is shown.

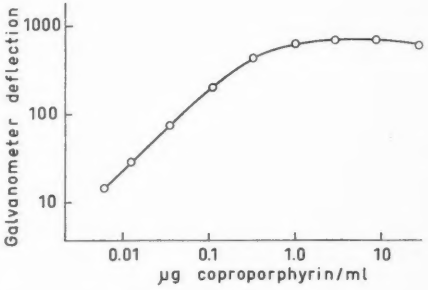

Fig. 5. The relation between coproporphyrin concentration and fluorescence intensity. Solvent: 0.2 *N* HCl.

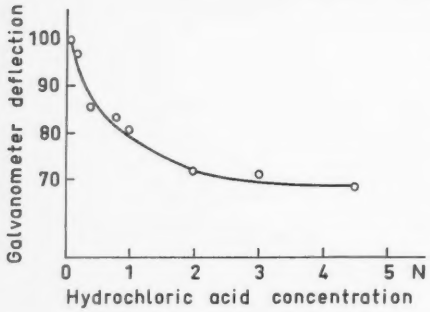

Fig. 6. The relation between coproporphyrin fluorescence and the concentration of hydrochloric acid in the solvent. 0.027 μg coproporphyrin/ml.

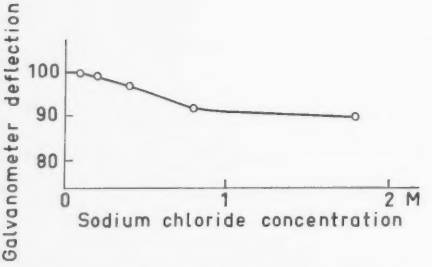

Fig. 7. The relation between coproporphyrin fluorescence and the concentration of sodium chloride in the solvent. 0.027 μg coproporphyrin/ml, dissolved in 0.2 *N* HCl.

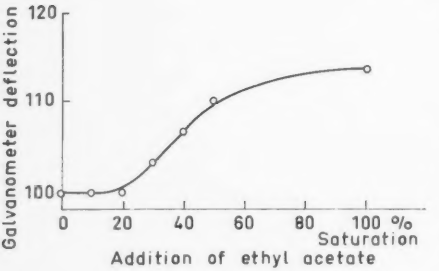

Fig. 8. The relation between coproporphyrin fluorescence and the degree of saturating the solvent with ethyl acetate. Room temperature. 0.027 μg coproporphyrin/ml, dissolved in 0.2 *N* HCl.

Ethyl acetate and acetic acid concentrations. The influence of different concentrations of ethyl acetate was studied using a 0.2 *N* HCl solution of 0.027 μg coproporphyrin/ml (Fig. 8). When the solution was saturated with ethyl acetate at room temperature, the fluorescence increased about 12 %. This was found to be true for other coproporphyrin concentrations as well. Addition of glacial acetic acid up to 20 % (*v*/*v*) was also studied and an increased fluorescence was noted (Fig. 9).

Fluorescence at varying pH. The influence of pH on fluorescence is difficult to evaluate owing to the double influence of buffers; pH as well as the individual constituents of the buffer may quench or enhance the intensity. In the present experiments, the desired pH was obtained by partial neutralization of HCl by sodium acetate. In this manner, conditions similar to those in the final 0.24 *N* HCl extracts were achieved. The fluorescence was found to be essentially unchanged between pH 0.85–1.2. The fluorescence was depressed markedly in solutions with pH higher than 1.7. In the final 0.24 *N* HCl extracts from a complete analysis, pH was found to be approximately 1 (Fig. 10).

Discussion

Emission and activation spectra. The present study seems to be the first report on the emission and activation spectra of proto- and coproporphyrin measured with a photoelectrical spectrofluorometer. When comparing with the earlier investigation on porphyrin emission spectra by Bois (1927), it is interesting to note that, in the present investigation, only one emission band could be found: the

maxima for proto- and coproporphyrin being 595 and 590 mμ, respectively. In the study of Bois, at least two bands were found (cf. Table 5). The explanation of this discrepancy is not clear. Obviously the emission spectra of proto- and coproporphyrin as obtained by the author's technique do not differ enough to permit a simultaneous estimation of the two porphyrins.

Earlier investigations of the activation spectra of copro- and protoporphyrin are limited to reports of the most favorable wavelength-regions for the activation of fluorescence. Thus Borst and Königsdörffer (1929) found the region 280–470 mμ and Bois (1927) 340–470 mμ to be most favorable. The present finding of sharp peaks in the activation spectra at the same wavelengths as the peaks of the different Soret bands are what could be expected from a theoretical point of view (Table 6). Accordingly, maximal fluorescence of pure proto- and coproporphyrin in 0.2 *N* HCl was elicited by light of the wavelengths 407 and 399.5 mμ.

Guided by these experiments, the routine fluorometric estimation was carried out in the following manner. The fluorescence was activated by the 404 mμ Hg line, isolated by the monochromator. The emitted light was separated from scattered light by a filter, transmitting less than 0.05 % at the wavelength of the activating light; 0.2 % at 509 mμ, 79 % at 546 mμ and 98 % at 578 and 644 mμ (Jena OG 1).

The concentration of the porphyrin. Fikentscher (1932) and Schwartz, Zieve and Watson (1951) have studied the relationship between fluorescence intensity and coproporphyrin concentration. In both

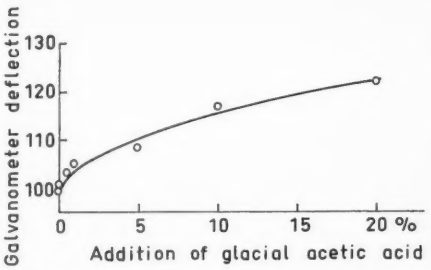

Fig. 9. The relation between coproporphyrin fluorescence and the concentration of acetic acid in the solvent. 0.027 μg coproporphyrin/ml, dissolved in 0.2 *N* HCl.

studies, a linear relation was found up to 0.5 and 0.05 μg/ml, respectively. Higher concentrations were followed by a deviation from linearity and finally by quenching of the fluorescence. The present finding of a linear relationship up to 0.1 μg/ml is confirmatory. The differences are probably due to differences in the fluorometers.

The influence of the solvent. Fluorescence intensity of coproporphyrin dissolved in hydrochloric acid, acetic acid and saline of various concentrations and the effect of saturating the solvent with

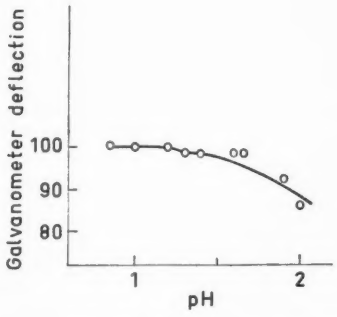

Fig. 10. The relation between coproporphyrin fluorescence and pH. 0.2 *N* HCl solutions were partially neutralized by 0.2 *M* sodium acetate to the desired pH. 0.013 μg coproporphyrin/ml.

TABLE 5. *Fluorescence emission bands of some porphyrins dissolved in 2 N HCl.* (Bois, 1927)

Band	I	II	III
Protoporphyrin	654		603
Coproporphyrin	652	618	595
Hematoporphyrin	653	619	597

Band I was stronger than bands II and III.

ethyl acetate has been only incompletely studied earlier. Schwartz, Zieve and Watson (1951) noted the suppression of coproporphyrin fluorescence in 1.5 *N* HCl compared to that in 0.3 *N* HCl; the ratio of fluorescence in 0.3 *N*/1.5 *N* HCl ranged between 1.10–1.20. Recently, Chu and Chu (1959) have published a study of porphyrin in which the coproporphyrin's fluorescence in varying HCl-concentrations was studied. According to the figures in their paper, the suppression of fluorescence was similar to the present findings.

The enhancement of the fluorescence when coproporphyrin solutions are saturated with ethyl acetate is important for the analysis of free erythrocyte coproporphyrin since ethyl acetate is always present in the final HCl-extracts. The present finding of a 12 % enhancement of the fluorescence of coproporphyrin dissolved in 0.2 *N* HCl is slightly higher than the 8 % enhancement found by Schwartz, Zieve and Watson (1951). However, the latter authors studied coproporphyrin dissolved in 1.5 *N* HCl. This may explain the difference.

The influence of various ions on the intensity of the porphyrin fluorescence is seldom mentioned in the literature. Fischer and Orth (1937) state that phosphate and citrate ions increase the fluorescence. Thus fluorescence-pH curves obtained by aid of Mac-Ilvaine's buffer published by Fink and Hoerburger (1935) and by Chu and Chu (1959) are not readily interpreted.

In the present experiments, mixtures of HCl and sodium acetate were used. The fluorescence was constant between pH 0.85–1.2, showing that the estimation of coproporphyrin is made under favorable pH conditions (pH of the final extracts being about 1). These findings do not completely agree with the findings of Jope and O'Brien (1945) who found a maximum fluorescence at pH 1.5. However, they do not state the composition of their buffers, and the results are therefore not comparable.

TABLE 6. *Wavelengths for maximum excitation of fluorescence compared to the wavelengths for maximum light absorption.*

	Coproporphyrin		Protoporphyrin	
	0.2 *N* HCl	2 *N* HCl	0.2 *N* HCl	2 *N* HCl
Maximum excitation	399–400	401	407	409
Maximum absorption	400	401–402	405	408

CHAPTER III

Losses of porphyrin during the analysis

During the preliminary experimental work it was found that losses of porphyrin occurred during the purification procedure. This was mainly due to the destruction of protoporphyrin by light and the formation of metal complexes of coproporphyrin. In addition to these findings, some other experiments are described concerning the stability of protoporphyrin in concentrated acid and the possible presence of reduced porphyrins in the erythrocyte samples.

1. Light sensitivity of protoporphyrin

The light sensitivity of protoporphyrin has long been known, and was noted by Lageder (1936) and by Grinstein and Watson (1943). The degradation products of protoporphyrin are illdefined and do not exhibit the same strong fluorescence and light absorption as the intact porphyrin. Thus porphyrin appears to be lost during the analysis.

To determine if the light sensitivity of protoporphyrin was important for the present work a series of experiments was performed (Tables 7 and 8). Equal amounts of protoporphyrin were dissolved in 1 *N* HCl and in ethyl acetate and left in diffuse daylight behind double layers of ordinary window-glass. After three hours, almost all protoporphyrin dissolved in the ethyl acetate and 90 % of protoporphyrin dissolved in HCl had disappeared when compared with controls kept in the dark. A corresponding experiment was performed, testing the stability of protoporphyrin kept in the dark and of protoporphyrin exposed to the subdued light from electric bulbs as used in the routine work. In this case no deterioration of the porphyrin could be detected (Table 7).

The importance of avoiding daylight was also studied by performing the complete analysis on samples of the same blood, at one occasion in strong daylight and at another occasion in subdued light from electric bulbs. When the analyses were performed in daylight, considerable loss of protoporphyrin occurred, as can be seen from Table 8. There was also a slight increase of the "coproporphyrin fraction".

TABLE 7. *The influence on light on the stability of protoporphyrin.*

	Solvent	
	1 *N* HCl μg	Ethyl acetate μg
After 3^h in daylight	0.16	0.04
Control	1.40	1.20
After 3^h in incandescent light	1.55	1.31
Control	1.53	1.32

TABLE 8. *Analyses of free erythrocyte proto- and coproporphyrin during different light conditions. Four analyses of each sample of erythrocytes.*

	Protoporphyrin μg/100 ml RBC	Coproporphyrin μg/100 ml RBC
Strong daylight	4, 6, 10, 13	1.8, 2.9, 1.7[a]
Incandescent light	21.5, 21.5, 22.1, 24.5	0.9, 1.0, 0.8, 1.1

[a] one analysis was lost.

This is explained, perhaps, by accelerated formation of hematoporphyrin-like pigments.

In order to minimize protoporphyrin loss due to light destruction, the analyses were performed in subdued light from electric bulbs. Daylight was avoided as far as possible. During intermissions in the analytical work, separating funnels and other vessels containing porphyrin solutions were covered with black cloth.

2. The possible formation of metal complex

Porphyrins are known to form complexes with metals. Oliver and Rawlinson (1951) studied a copper complex of coproporphyrin. Since this complex does not fluoresce, the complex formation was used for the quantitative estimation of small amounts of coproporphyrin. Zinc also forms complexes very readily with porphyrins. Brugsch (1959) states that the complexes are formed even at normal temperature and in dilute acid solutions. Thus serious errors in the determination of minute amounts of coproporphyrin can be introduced.

In the present investigation, it was found difficult to obtain quantitative recovery of coproporphyrin added to ethyl acetate and subsequently extracted by dilute hydrochloric acid. It was suspected that a formation of porphyrin-metal complexes had occurred although the presence of metals could not be proved. The addition of EDTA[1] to all batches of ethyl acetate was followed by satisfactory recoveries and no untoward effects could be observed. The EDTA was added in substance to the ethyl acetate, shaken and allowed to settle. The ethyl acetate was then decanted.

3. Protoporphyrin degradation in strong acid

Schumm (1927) established that protoporphyrin dissolved in strong acid is partially transformed into hematoporphyrin. According to Paul (1953), it is possible that this transformation occurs via an intermediate; i.e., monovinyl, monohydroxyethyl, tetramethyl, porphin dipropionic acid. The hematoporphyrin is extracted in the coproporphyrin fraction and may introduce severe errors in the estimation of free erythrocyte coproporphyrin. There does not seem to exist any practical method for the separation of hemato- and coproporphyrin in these small concentrations (Brugsch 1959). During the analysis of free erythrocyte proto- and copropor-

[1] "Titriplex III", the disodium salt of ethylenediaminotetraacetic acid.

phyrin, rather concentrated hydrochloric acid has to be employed; thus it was considered important to try to ascertain if protoporphyrin was transformed to hematoporphyrin or hematoporphyrin-like pigments during the analysis. This was thought to be particularly important since studies of this kind had not been reported earlier.

Protoporphyrin dimethyl ester was hydrolyzed overnight in 7 *N* HCl, and subsequently diluted to 1 *N* HCl. In order to remove all traces of hematoporphyrin and other pigments with low HCl-numbers, the protoporphyrin was purified by repeated distributions between 0.24 *N* HCl and ethyl acetate according to the principles of Paul (1953). The protoporphyrin goes into the ethyl acetate phase, and the hematoporphyrin-like pigments accumulate in the hydrochloric acid. This purification was done immediately before the protoporphyrin was added to the first stage of the complete analysis. Ten experiments of this kind were carried out. The added amounts corresponded to 10–250 μg % free erythrocyte protoporphyrin. After performing all the usual steps of the analysis, protoporphyrin and "coproporphyrin" were determined in the routine manner. The "coproporphyrin" fractions showed a fluorescence which would indicate -0.006 to $+0.028$ μg coproporphyrin (owing to the error of the fluorometric analyses, some results were "negative"). Cf. Table 9.

Discussion. It has not been possible to study in closer detail the formation of hematoporphyrin from protoporphyrin. Probably a number of other degradation products are formed in addition to hematoporphyrin. However, when relatively small amounts of protoporphyrin (less than 3 μg, corresponding to about 100 μg % free erythrocyte protoporphyrin) are present, only insignificant amounts of coproporphyrin-simulating fluorescence appears in the 0.24 *N* HCl extracts. The coproporphyrin values become too high with blood samples containing more than about 100 μg % protoporphyrin. The increase has the magnitude of 0.3–0.4 μg % coproporphyrin per 100 μg % protoporphyrin.

TABLE 9. *Protoporphyrin degradation to hematoporphyrin-like pigments.*

Protoporphyrin found, μg	Fluorescence in 0.24 *N* HCl extracts corresponding to coproporphyrin, μg
0.35	+ 0.003
0.41	− 0.0007
0.59	− 0.006
0.77	− 0.0015
0.98	+ 0.012
1.21	+ 0.0005
3.14	+ 0.0025
3.18	+ 0.012
6.27	+ 0.028
6.28	+ 0.026

4. Reduced porphyrins

Fischer, Bartholomäus and Röse (1913) established that reduction of a porphyrin with sodium amalgam yields a colorless substance which easily could be reoxidized by air. Studying the porphyrin in urine, Watson, de Mello, Schwartz, Hawkinson and Bossenmaier (1951) found a coproporphyrin precursor similar to a reduced coproporphyrin. The precursor was easily extracted by ethyl acetate but from this solution only insignificant amounts could be extracted by hydrochloric acid. The precursor was completely oxidized by

TABLE 10. *Comparison of porphyrin yield from samples of erythrocytes analyzed with and without iodine wash.*

	Number of pairs	Mean results μg/100 ml RBC Without I_2-wash	With I_2-wash
Protoporphyrin	11	26.4	27.7
Coproporphyrin	13	1.3	1.1

dilute iodine solutions. Neve, Labbe and Aldrich (1956) and, later on, several other investigators have demonstrated that not the porphyrins themselves but the reduced analogues of uro- and coproporphyrin are intermediates in the synthesis of protoporphyrin and heme. The reduced analogues are often called "porphyrinogens".

During the study of the method for the estimation of free erythrocyte proto- and coproporphyrin, it was considered important to try to demonstrate the presence or absence of porphyrinogens in the erythrocytes—particularly coproporphyrinogen. In accordance to the findings of Watson *et al.* (1951) the ethyl acetate/glacial acetic acid extract of the erythrocytes was washed with a fresh aqueous solution of iodine (0.005 %) in order to oxidize any porphyrinogens present. Duplicate samples of blood from healthy individuals were studied and analyzed with the routine method adopted by the author as well as with this method completed with the iodine wash. Results are found in Table 10. No significant differences were found.

This result cannot be taken as evidence of the absence of porphyrinogens in the erythrocytes since the porphyrinogens are known to be easily autoxidized when exposed to air. During the course of the extraction procedure, such oxidation may easily have taken place. However, the results indicate that no porphyrinogens escape the analysis as was the case in the urine analysis of Watson *et al.* (1951).

CHAPTER IV

Extraction and purification of free erythrocyte copro- and protoporphyrin

1. Extraction of the erythrocytes

In the first step of the analysis, the erythrocytes are treated with a mixture of ethyl acetate and glacial acetic acid in order to extract the free porphyrins. The precipitate formed is thoroughly mixed with the extraction mixture. The extract is removed by filtration and the precipitate washed three times by small amounts of the extraction mixture.

In an attempt to ascertain the efficiency of the extraction of free erythrocyte porphyrins, the following experiment was performed. Samples of erythrocytes were extracted as described above and the content of free proto- and coproporphyrin determined. In order to find out if the precipitate still contained porphyrin, a second extraction was performed in the same manner. The free protoporphyrin in the second extraction was found to be 2–5 % of that of the first extraction. The free coproporphyrin in the second extraction appeared to be insignificant (Table 11).

The result of these experiments indicates that no important amount of proto- or coproporphyrin remains in the precipitate after one routine extraction. This is in accordance with the results of Ward and Mason (1950) who in a similar experiment found 2–3 % in the second extract. These authors did not study the coproporphyrin content of the erythrocytes.

2. Possible formation of free protoporphyrin from hemoglobin

According to Schumm (1924), protoporphyrin is split off from hemoglobin much more easily than from oxyhemoglobin. In a later paper (1939), the same author emphasized the importance of using oxygenated blood for the analysis of free porphyrin in plasma. The necessity of a similar precaution is not mentioned in the discussion of the analysis of free erythrocyte porphyrin (1939) although in the earlier paper (1924) it is reported that porphyrin can be obtained in great amounts from blood which had been stored in sterile vessels at room temperature until it acquired the colour of reduced hemoglobin.

A formation of protoporphyrin from hemoglobin during the analysis of free red-cell porphyrin might form a serious source of error. Van den Bergh and Hyman (1928) tried to disprove the possibility of protoporphyrin formation by extracting crystalline hemoglobin. No protoporphyrin was found in the extract. Later,

TABLE 11. *Repeated extraction of a number of erythrocyte samples.*

Erythrocyte sample number	Porphyrin in the first extract μg	Porphyrin in the second extract μg	Porphyrin in second extract in per cent of first extract
Protoporphyrin			
1	0.96	0.02	2.1
2	1.16	0.05	4.3
3	1.17	0.05	3.6
4	1.61	0.08	5.0
5	4.51	0.17	3.8
6	5.44	0.16	2.9
Coproporphyrin			
7	0.011	+0.0016	—
8	0.049	−0.002	—
9	0.052	0.000	—

several authors have discussed the possibility of protoporphyrin formation from hemoglobin during the analysis—most thoroughly perhaps Bénard, Gajdos and Canivet (1949). However, the risk was considered insignificant. According to Brugsch (1959), the risk of protoporphyrin formation from hemoglobin is most important when blood or parts of organs from corpses are extracted by mineral acids.

During the present work, determinations of free protoporphyrin were performed on four samples of blood, two of which had been repeatedly shaken in nitrogen atmosphere and two shaken in air. No difference was found between the two pairs when subsequently analyzed for the presence of free protoporphyrin. In the present investigation, as in those of most authors, no special precautions were taken to ensure maximum oxygenation of the blood sample.

3. The distribution of porphyrin between ethyl acetate and hydrochloric acid

The distribution of porphyrins between ether and hydrochloric acid at varying concentrations of the latter is often given by their "HCl-number". The "HCl-number" is defined as the concentration of hydrochloric acid in per cent which from an equal volume of ether solution of a porphyrin extracts two-thirds of the porphyrin. The "HCl-number" of protoporphyrin is 2, of coproporphyrin 0.09 and of hematoporphyrin 0.1. When porphyrins are distributed between ethyl acetate and hydrochloric acid, the corresponding HCl-numbers are higher. Under the conditions employed in the present study, they were found to be 8 for protoporphyrin and 0.4 for coproporphyrin. More concentrated acid is thus necessary for extractions from ethyl acetate than from ether. Ethyl acetate was preferred for various practical reasons. Schwartz and Wikoff (1952), in their method for the determination of free erythrocyte copro- and protoporphyrin, also use ethyl acetate instead of ether.

Considering the HCl-numbers of proto- and coproporphyrin, the separation would be expected to be easy. However, the fact that protoporphyrin occurs in much higher concentrations than those of coproporphyrin (about 20–50 μg protoporphy-

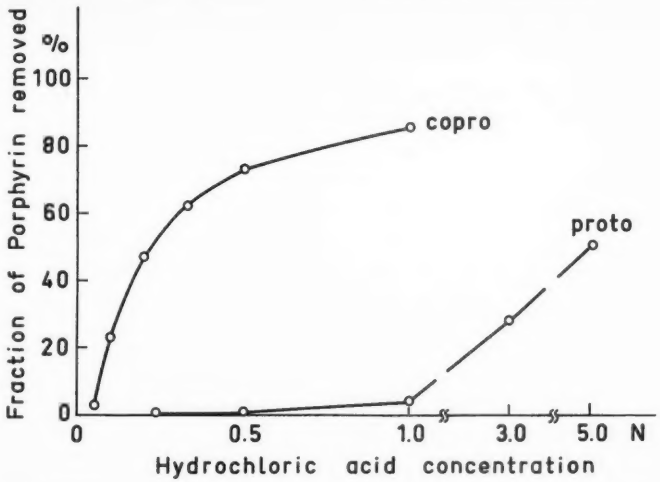

Fig. 11. The fraction of copro- or protoporphyrin removed from 150 ml water-saturated ethyl acetate solution by one extraction with 4 ml HCl of different concentrations.

rin and about 0.5–2 μg coproporphyrin per 100 ml erythrocytes) makes the selection of a suitable HCl-concentration very important.

The distribution of proto- and coproporphyrin between water-saturated ethyl acetate and hydrochloric acid was further studied. The volumes of the two solvents were chosen to be similar to those used in the final extraction of porphyrins from ethyl acetate solution by Schwartz and Wikoff (1952). The exact volumes of solvents are not stated in their paper which makes a strict comparison impossible. The volumes were equal to those used for the routine determination of erythrocyte proto- and coproporphyrin (150 ml ethyl acetate are extracted by 4 ml hydrochloric acid, cf. p. 12). Known amounts of copro- or protoporphyrin were added to the water-saturated ethyl acetate. Extraction was performed once by hydrochloric acid. The extracts were made up to the same volume and adjusted to the same HCl concentration by adding water and HCl. The amounts extracted were calculated according to With (1955) after measuring the absorption in near ultraviolet. The experiments revealed (Fig. 11) that relatively high concentrations of HCl are necessary to obtain a satisfactory removal of the porphyrins by a limited number of extractions.

Discussion

Protoporphyrin. Earlier workers have used a wide range of HCl concentrations for the extraction of protoporphyrin. Thus in the original description by van den Bergh (1928), 5 % HCl (about 1.7 *N*) is recommended, while Schumm (1939) uses the more efficient 25 % HCl (about 8 *N*) for extraction. Schwartz and Wikoff (1952) use 3 *N* HCl. In the present investigation, the latter concentration was found rather inefficient; at least 5 *N* HCl had to be ap-

plied in order to avoid too many extractions. Higher concentrations of the acid were not used in order to minimize the formation of hematoporphyrin-like pigments.

Coproporphyrin. For the extraction of coproporphyrin in the presence of protoporphyrin, it is important not to use too high acid concentrations in order to avoid unnecessary co-extraction of protoporphyrin. Schwartz and Wikoff (1952) used 0.1 *N* HCl, but this concentration obviously extracts too small fractions of the coproporphyrin. In spite of the high dilution of the acid, traces of protoporphyrin were extracted and had to be removed by washings with chloroform. About 50 % of the coproporphyrin is removed by one extraction with 0.24 *N* HCl; simultaneously 0.25 % or slightly less of the protoporphyrin is co-extracted. Since the ratio between proto- and coproporphyrin generally is 20–40/1, sometimes 100/1, ¼ to ½ of the fluorescence of the 0.24 *N* HCl extracts can be expected to come from protoporphyrin. It was not considered advisable to increase this fraction by using stronger concentrations of the acid.

According to the theory of distribution, only one extraction under controlled conditions ought to be necessary; and the total amount of porphyrin can be calculated by aid of distribution coefficients. However, calculations based on distribution coefficients cannot be strictly applied here. The water in the water-saturated ethyl acetate dilutes the acid. During routine conditions 5 *N* HCl was diluted to about 3 *N* and 0.24 *N* HCl to about 0.20 *N*. The separation of the two phases takes a long time to be perfect. A small but significant amount of the acid extract is left in the stopcock and often also in droplets on the walls of the funnel. Even if four consecutive extractions are made, it is always necessary to carry out the analysis with a carefully standardized technique in order to obtain satisfactory reproducibility.

Removal of protoporphyrin from coproporphyrin solutions by chloroform extractions. Schwartz and Wikoff (1952) recommend the washing of the coproporphyrin extracts by chloroform "to remove traces of chloroform-soluble porphyrins". Trying this method, the present author found it troublesome, disturbing the subsequent fluorometric estimation of coproporphyrin and also rather inefficient even if large amounts of chloroform were used. The ratio between the volumes used by Schwartz and Wikoff is not given exactly, but probably about 0.25 volume of chloroform to one volume of the 0.1 *N* HCl extract has been used. During the present study, the effect of washing with 0.5 volume of chloroform was tried. Only 45 % of the protoporphyrin was removed by each washing and more than three washings would be necessary to remove at least 85 % of the protoporphyrin.

4. The background fluorescence and the correction for traces of protoporphyrin in the final 0.24 *N* HCl extracts

When small intensities of fluorescence are studied, attention must be paid to the possible presence of a background reading on the galvanometer in addition to the usual "dark current" reading. This background is composed of scattered light and of fluorescence that does not come from the investigated fluorescent substance. Considerable reduction of the background

may be achieved by using the purest chemicals, perfectly clear test solutions, and by extreme cleanliness when handling the cells and other parts of the optical system. Also, to diminish the effects of the scattered light, it is very important to choose suitable wavelength-ranges of the exciting and emitted light.

Paying attention to the factors mentioned above, the background galvanometer readings were studied in some solvents. (The galvanometer was adjusted to zero when the exciting light was shut off.) As can be seen from Table 12, the background readings of distilled water and dilute hydrochloric acid are negligible, while that of ethyl acetate is more noticeable. Re-distillation *in vacuo* diminished the background of ethyl acetate to 50 %. Dilute hydrochloric acid saturated with ethyl acetate showed a moderate background that was not noticeably diminished by re-distilling the ethyl acetate.

In the final extracts of the analysis of free erythrocyte coproporphyrin, the intensity of the background fluorescence was found difficult to estimate, since it appeared to vary from one analysis to another. When attempting to measure quantitatively the fluorescence of coproporphyrin, another difficulty was encountered, viz. the presence of protoporphyrin in the 0.24 *N* HCl extracts. Attempts to remove the protoporphyrin by washing with chloroform according to Schwartz and Wikoff (1952) had not been successful and some other method was sought for. The combined problem of correcting for the background and the protoporphyrin fluorescence was studied from various aspects, and finally the following procedure was adopted. Six consecutive extractions are performed with 0.24 *N* HCl. According to earlier experiments each extraction removes about 50 % of the coproporphyrin and less than 0.25 % of the protoporphyrin present in the ethyl acetate solution. The sixth extract is practically free from coproporphyrin and the fluorescence of that extract is taken as a measure of the background and of the protoporphyrin fluorescence. Assuming that the protoporphyrin and the factors giving rise to the background fluorescence are constant in the six consecutive extracts, the coproporphyrin fluorescence can be calculated.

TABLE 12. *"Fluorescence's background" of some solvents.*

Solvent	Equivalent to coproporphyrin $\mu g \cdot 10^{-3}$/ml
Distilled water	1.5
0.2 *N* HCl	2
Ethyl acetate	10
Ethyl acetate, distilled in vacuo	5
0.2 *N* HCl, saturated with ethyl acetate	3.5
0.2 *N* HCl saturated with distilled ethyl acetate	3.5

The sixth extract is not, of course, completely free of coproporphyrin; however, the amount can be calculated as follows. Let k be the fraction of coproporphyrin that remains in the ethyl acetate phase after one extraction with hydrochloric acid. After two extractions, k^2 remains and after six extractions k^6. Correspondingly, in the sixth hydrochloric acid extract a fraction $k^5(1-k)$ appears. During the conditions used in the analysis, k is approximately equal to 0.5. If k equals 0.50, the first five hydrochloric acid extracts contain a total of 97 % and the sixth extract 1.56 % of the coproporphyrin. If the last extract is considered copropor-

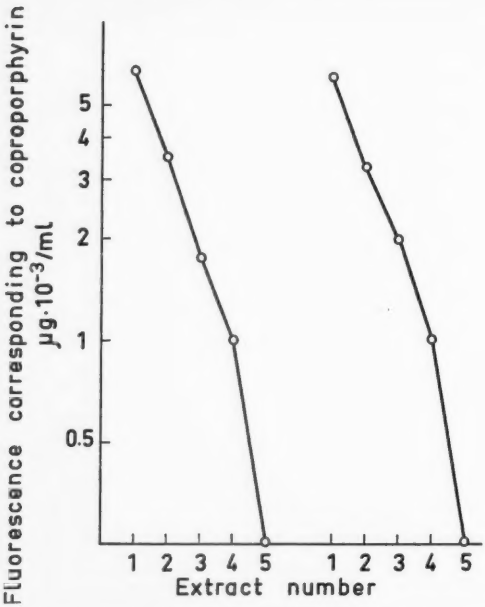

Fig. 12. Fluorescence intensities in the six consecutive 0.24 *N* HCl extracts. The fluorescence of the sixth extract was subtracted from the fluorescence of each of the preceding extracts. Two different samples of erythrocytes.

phyrin-free an error of 1.56 × 7 or 10.9 % is introduced and the calculated amount of coproporphyrin is about 89 % of the true amount.

The error introduced in the determination of coproporphyrin by the assumption that protoporphyrin fluorescence is constant in the consecutive extracts is very small. If 0.250 % of the protoporphyrin goes into the first hydrochloric acid extract, the sixth extract will contain 0.247 %. Even if the free erythrocyte protoporphyrin is high, e.g. 300 µg %, the result of the free erythrocyte coproporphyrin analysis is only increased about 0.03 µg %.

Of course, these calculations are only valid if the distribution coefficients for proto- and coproporphyrin, the fluorescence from other substances and the light scattering are constant. In practice, the experimental results supported the theoretical consideration. The calculated intensity of the coproporphyrin fluorescence plotted against the extraction number yielded almost straight lines on a semi-logarithmic diagram (Fig. 12).

5. The enhancement of fluorescence in the six consecutive 0.24 *N* HCl extracts

The method adopted for the determination of coproporphyrin is justified only if, in addition to the enhancement caused by ethyl acetate, no other factors influence the intensity of the fluorescence of the six extracts. In order to study this question, the following experiment was carried out. Six samples of normal erythrocytes were examined by the routine ana-

TABLE 13. *The enhancement of fluorescence by the 0.24 N HCl extracts.*

Ordinal number of extract	Expected increase of fluorescence Arbitrary units	Observed increase of fluorescence Arbitrary units
1st	100	102
2nd	100	115
3rd	100	112
4th	100	115
5th	100	108
6th	100	108

lysis of free erythrocyte proto- and coproporphyrin. The first 0.24 *N* HCl extracts from the six analyses were pooled, the second extracts pooled, and so on. The fluorescence of the contents of each of the pools was measured and a small volume of a standard coproporphyrin solution added. The fluorescence increase was then measured and compared with the expected increase. The background fluorescence was small compared to the fluorescence brought about by the addition.

In all extracts, the coproporphyrin fluorescence increased more than expected. In the first extract, this was less pronounced than in the subsequent ones (Table 13). If no other factor than the saturation with ethyl acetate was responsible, the observed fluorescence should be 12 % higher than the expected (cf. p. 20). This would also be the case in the last five extracts. An increased NaCl concentration in the first extract is one possible cause of the less pronounced enhancement of the fluorescence in the first extract. Since the fluorometric estimation was always corrected for the 12 % enhancement of the coproporphyrin fluorescence, the less pronounced enhancement in the first extract causes a total underestimation of coproporphyrin by 4–5 %.

6. Blank values of the complete determination of free erythrocyte proto- and coproporphyrin

During the methodological studies, methods were elaborated for the reduction of the influence of impurities and other "blank" factors. In an attempt to ascertain if these factors were, in fact, satisfactorily reduced, ten "blank" determinations were performed without any addition of erythrocytes or plasma. As can be seen from Table 14, the "blank" light absorption of the 5 *N* HCl extracts was negligible, corresponding on the average to 0.02 μg protoporphyrin. Even when using the method described earlier (p. 31) for the correction of the fluorometrical determination of coproporphyrin, fluorescence intensities were found in the 0.24 *N* HCl extracts corresponding on the average to 0.0056 μg coproporphyrin.

Earlier, the presence of "blanks" in the determination of free erythrocyte proto-

TABLE 14. *Results of ten blank determinations of free erythrocyte proto- and coproporphyrin.*

	Light absorption corresponding to protoporphyrin μg	Fluorescence corresponding to coproporphyrin μg
Range	-0.025 to $+0.055$	$+0.0011$ to $+0.0094$
Mean $\pm e\,(M)$	0.02 ± 0.008	0.0056 ± 0.0009

porphyrin has been described by Sturgeon (1954). With his method, the mean light absorption equalled 4 μg protoporphyrin. With the present method, a negligible protoporphyrin "blank" was found. This favorable result is thought to be due to the use of the Rimington–Sveinssen correction (p. 14). No correction for the small protoporphyrin "blank" has been performed.

However, in the determination of coproporphyrin, a "blank" was found that could not be disregarded. The cause of this "blank" is not clear. In most cases, the "blank" has been found to be due to an "extra fluorescence" appearing in the first extract. It is probable that the "fluorescence" of this extract contains more scattered light than the rest. Thus the blank correction made by the subtraction of the "fluorescence" in the sixth extract becomes insufficient. It should be noted, that in the experiment just described (Table 13), the "extra fluorescence" was very small compared to the fluorescence of the added coproporphyrin. In Fig. 12, p. 32, the "extra fluorescence" is not observed since its effect is opposed by the depressing of the fluorescence in the first extract.—In all determinations, the sum of the coproporphyrin fluorescence in the first five extracts was corrected by subtracting 0.0056 μg.

CHAPTER V

Evaluation of the method

1. Recovery experiments

Recovery experiments were made as follows: Hydrochloric acid solutions of copro- or protoporphyrin were partially neutralized with sodium acetate. The porphyrins were transferred quantitatively into ethyl acetate. Aliquots of the ethyl acetate solution were added to the mixture of ethyl acetate and glacial acetic acid used for the extraction of erythrocytes. In some cases, the recovery from pure solutions without erythrocytes was also studied. The volumes of the added solutions were small compared to the volume of the ethyl acetate/acetic acid mixture. The analysis was completed and the recovery of the added porphyrin calculated. In separate samples of the erythrocyte, the preformed content of free porphyrins was determined.

Results

Table 15 shows the results of coproporphyrin and protoporphyrin additions. The coproporphyrin recoveries ranged between 51 and 90 %, averaging 74 %. Protoporphyrin recoveries varied between 68 and 91 %, averaging 78 %. Slightly higher recoveries of coproporphyrin were obtained from the additions to pure solutions than from additions to erythrocyte extracts. In contrast, the recoveries of protoporphyrin additions to erythrocytes extracts were better than the recoveries from pure solutions.

Discussion

Recovery experiments of free erythrocyte copro- and protoporphyrin, independently, have apparently not been reported earlier. Schwartz and Wikoff (1952) who have described the only method to date, do not list any recovery experiments. However, these experiments have been carried out in the analysis of free erythrocyte porphyrin without differentiation between copro- and protoporphyrin. Since most of the erythrocyte porphyrin consists of protoporphyrin, a comparison may be made with the present recovery experiments with protoporphyrin.

The method of Grinstein and Wintrobe (1948) has been investigated by them and also by Ventura (1954 a). The highest recovery of added protoporphyrin was reported by Ventura, averaging 92 %. Grinstein and Wintrobe recovered 84–96 %, averaging 90 %. The latter authors also studied the recovery of protoporphyrin added to pure solutions, and similar results were obtained.

In the present author's experiments, the recoveries are somewhat lower. However,

TABLE 15. *The recovery of added copro- and protoporphyrin.*

Exp. No.	Preformed porphyrin μg	Added porphyrin μg	Porphyrin found μg	Recovery of added porhyrin μg	Per cent added porphyrin recovered
Coproporphyrin					
1	—	0.054	0.045	0.045	83
2	—	0.108	0.086	0.086	79
3	—	0.162	0.135	0.135	81
4	0.025	0.054	0.065	0.040	74
5	0.025	0.108	0.082	0.057	53
6	0.025	0.162	0.112	0.087	54
7	0.038	0.200	0.208	0.170	85
8	0.038	0.400	0.370	0.332	83
9	0.038	0.600	0.580	0.542	90
10	0.036	0.200	0.139	0.103	51
11	0.036	0.400	0.343	0.307	77
12	0.036	0.600	0.532	0.496	83
Protoporphyrin					
13	—	0.40	0.28	0.28	70
14	—	0.80	0.54	0.54	68
15	—	1.20	0.92	0.92	74
16	1.00	0.65	1.59	0.59	91
17	1.00	1.29	2.14	1.14	87
18	1.00	1.94	2.69	1.69	86
19	0.85	0.65	1.31	0.46	71
20	0.85	1.29	1.77	0.92	71
21	0.85	1.94	2.50	1.65	85

the methods are not fully comparable. Grinstein and Wintrobe used ethyl ether instead of ethyl acetate in the purification of the porphyrin. In addition, they estimated the protoporphyrin content by measuring the maximum light absorption in the Soret band, while in the present study the correction suggested by Rimington and Sveinssen is used.

The expected losses of protoporphyrin during the analysis according to the present method can be estimated to 15–20 %, viz. 6–7 % at each of the two extractions of the organic solvent by acid and a few per cent or less at the other extractions and washings. Thus the observed recovery, 78 %, is only slightly lower than the expected. The difference is probably dependent on inevitable light destruction. The fraction of protoporphyrin recovered varies between 68 and 91 %. This variation is consistent with the standard error of a single determination as calculated from 20 duplicate determinations of free erythrocyte protoporphyrin (see later). According to these analyses, the variance was 4.4. The variance of the present recovery experiments is 5.0.

The method described by Grinstein and Watson (1943) for the analysis of free erythrocyte porphyrin was modified by Schwartz and Wikoff (1952) to permit a simultaneous determination of copro- and protoporphyrin. The modification was based on a method intended for the analysis of *urinary* coproporphyrin described by Schwartz, Zieve and Watson (1951). This method involves extraction of the

coproporphyrin with buffered ethyl acetate washing with sodium acetate and finally extraction with 1.5 *N* HCl. No further purification was carried out. The amount of coproporphyrin was determined by a fluorometer. The recovery of added coproporphyrin was very satisfactory, averaging 100 %.

When this method was applied to the erythrocyte coproporphyrin, Schwartz and Wikoff (1952) introduced a purification step according to van den Bergh and Hyman and extracted the coproporphyrin from the ethyl acetate by 0.1 *N* HCl. These modifications tend to decrease the recovery of added coproporphyrin; and thus comparison of the recoveries should not be made between the present method and the method for the analysis of urinary coproporphyrin.

In the present method, the theoretical loss of coproporphyrin during the final extraction with 0.24 *N* HCl and the subsequent estimation has been calculated earlier to 15 %. The losses during the other steps in the analysis are small—less than a few per cent in each step. The theoretical recovery of the complete analysis is thus about 80 %. The recovery found when additions were made to pure solutions averaged 81 %. This would indicate that other losses were insignificant. However, when additions were made to extracts of erythrocytes, the recovery averaged 72 %. No certain explanation of this loss can be given. It may be partly due to formation of metal complexes.

In the determinations of free erythrocyte porphyrin, the results were corrected according to the findings in the recovery experiments. For practical reasons, the average *protoporphyrin* recovery was rounded off to 80 %. All results were therefore multiplied by a factor 1.25. In a similar manner, the results of determinations of free erythrocyte *coproporphyrin* were multiplied by 1.33.

In order to clarify the description of the calculations, the following example is described. Volume of the blood sample = 8 ml. Hematocrit = 35 %. Hence erythrocyte volume = 2.8 ml. Volume of combined 5 *N* HCl-extracts = 25 ml. Spectrophotometrical readings (5 cm cells): Extinction at the Soret band peak = 0.076, at 380 mμ = 0.022, at 430 mμ = 0.020. Hence $2E_{max} - E_{380} - E_{430}$ = 0.110. With's coefficient for protoporphyrin (1 cm cells) = 1.225. Hence protoporphyrin concentration = 0.027 μg/ml. Total volume of extracts 25 ml, and thus total protoporphyrin amount in extracts = 0.67 μg. Calculated protoporphyrin amount in sample = 0.84 μg (80 % efficiency of the analysis). Thus free erythrocyte protoporphyrin = 30 μg %. Fluorescence of the six 0.24 *N* HCl extracts = 16, 12.5, 11.5, 10.5, 10, 9.5 scale divisions, each corresponding to 0.5 $\mu g \cdot 10^{-3}$ coproporphyrin/ml. Fluorescence considered to be due to coproporphyrin = 6.5, 3, 2, 1.0, 0.5, 0 scale divisions. Volume of the first five extracts = 4.5, 5.0, 5.2, 4.8, 4.8 ml. Hence coproporphyrin content of the extracts = 14.6, 7.5, 5.1, 2.4, 1.2 $\mu g \cdot 10^{-3}$, in all 30.8 $\mu g \cdot 10^{-3}$. After subtraction of the blank of the complete determination (5.6 $\mu g \cdot 10^{-3}$), the total coproporphyrin amount in the extracts is 25.2 $\mu g \cdot 10^{-3}$. Calculated coproporphyrin in sample 33.6 $\mu g \cdot 10^{-3}$ (75 % efficiency of the analysis). Thus free erythrocyte coproporphyrin 1.2 μg %.

2. Error of the analysis

Duplicate analyses were performed on blood samples from 20 healthy subjects and on plasma samples from 10 subjects. Three to four ml of erythrocytes or 5 ml

plasma were used for each determination.[1] The standard error of a single determination of erythrocyte protoporphyrin was found to be ± 2.6 μg %; of erythrocyte coproporphyrin, ± 0.23 μg %; of plasma porphyrin, ± 0.25 μg %.

Discussion

The final error of analysis is probably composed of several factors such as: varying losses during the extraction and purification of the porphyrins; a certain destruction of the porphyrins by light, by strong acid or by metal complex formation; variations in the blank values; errors in the physical determination of the porphyrins in the final extracts. The two factors mentioned last have been possible to estimate, approximately. They were found to represent about one third of the total error of protoporphyrin analysis and about half the total error of coproporphyrin analysis.

Earlier reports about the errors in the analysis of free erythrocyte copro- and protoporphyrin have not been published. However, in three communications, the error of erythrocyte porphyrin analyses without differentiation of proto- and coproporphyrin has been studied. In the reports of Sturgeon (1954) and Koskelo (1959), the results are in agreement with those of the author. Sturgeon found a percentual standard error of ± 6 % and Koskelo an absolute standard error of ± 3 μg %. Ward and Mason (1950) report a very small standard error of ± 2.5 %. It is difficult to explain why the latter authors have obtained a so much better result since the methods of extraction and purification of the porphyrins were essentially identical. Sturgeon and Ward and Mason used the technique proposed by Grinstein and Watson (1943) and Koskelo the micro-modification by Grinstein and Wintrobe (1948). But the methods of estimating the porphyrin content in the final extracts were different. Ward and Mason measured the fluorescence intensity; Sturgeon studied the maximal light absorption in the Soret peak; and Koskelo also made readings of the light absorption at 380 and 430 mμ according to the principles of Rimington and Sveinssen (1950). According to the author's experience with free erythrocyte protoporphyrin, the fluorometric analysis is not more reliable than the spectrophotometric one, and therefore Ward and Mason's better results are difficult to explain.

3. The identification of the free erythrocyte porphyrins

During recent years, a number of intermediates in protoporphyrin and heme synthesis have been recognized. Not only are the reduced analogues of uro- and coproporphyrin intermediates, but there is also evidence of the participation of porphyrinogens with 3, 5, 6 and 7 COOH-groups (Granick and Mauzerall 1958 *a*, 1958 *b*). In disturbances of the protoporphyrin synthesis, porphyrin intermediates may accumulate in the erythrocytes. In one case of disturbed heme synthesis, Garby, Sjölin and Vahlquist (1957) found that the free erythrocyte coproporphyrin was increased. It is not improbable that other intermediates accumulate in the erythrocytes in other disturbances of the

[1] The difference between the results of the duplicate analyses appeared unrelated to the concentration of the porphyrin.

protoporphyrin synthesis. It is therefore desirable to identify the free porphyrins of the erythrocytes.

In the present method, the free erythrocyte porphyrins are extracted in two main fractions. The 5 *N* HCl fraction normally consists of protoporphyrin only and the 0.24 *N* HCl fraction is believed to contain coproporphyrin. However, since this separation is founded only on differences in the distribution coefficients, porphyrins with "HCl-numbers" close to or lower than that of coproporphyrin may be extracted in the 0.24 *N* HCl fractions together with coproporphyrin. Studies of the "HCl-number" for distribution between ethyl acetate and hydrochloric acid of porphyrins with 5, 6 and 7 COOH-groups (Chu and Chu 1959) have revealed that the "HCl-number" decreased when the number of COOH-groups increased. Thus all these porphyrins and uroporphyrin can be expected to appear in the 0.24 *N* HCl-extracts. The properties of the 3-COOH-porphyrin are essentially unknown, and it cannot be predicted in which fraction the main part of this porphyrin will appear.

Methods and experimental findings

5 N HCl extracts. In all analyses, the wave-length of the Soret band peak was noted and was always found at 409–410 mμ. A few analyses of the porphyrin in the extract were completed by paper chromatography according to Eriksen (1953). The individuals studied were normal adults, infants and cases of iron deficiency. In no case was a porphyrin other than protoporphyrin found[1]. A 3-COOH-porphyrin would probably not have escaped detection if the concentration were not too small since Nicholas and Rimington (1951) by paper chromatography were able to demonstrate the presence of a 3-COOH-porphyrin in the urine from a case of lead poisoning. Their method was very similar to Eriksen's method (1953).

[1] In some chromatograms, a fluorescent spot was seen just behind the solvent front. Since this spot occurred irregularly, it was considered to be an artifact.

TABLE 16. *Mean values of k in different groups.*

Group	Number of observations	*k*
Pure coproporphyrin	8	0.55
Erythrocytes from adults	10	0.53
Erythrocytes from newborns	10	0.58
Plasma from adults	10	0.54
Plasma from newborns	10	0.56
Erythrocytes from patients with iron deficiency	10	0.64

0.24 N Cl extracts. The distribution coefficient of the porphyrin in the 0.24 *N* HCl extracts has been studied in the following manner. Let k be the fraction of porphyrin that remains in the ethyl acetate after one extraction with 0.24 *N* HCl. If the amounts of a porphyrin in the consecutive extracts are $c_1, c_2, \ldots, c_n$, k equals c_2/c_1 or $c_n/c_{(n-1)}$. In the study, k could not be calculated by means of the porphyrin amounts in the three last extracts because in these the porphyrin concentration was too small. For the routine use, k was calculated from the expression $= \sqrt{c_3/c_1}$. Owing to errors in the fluorometric analyses, the k values will have, of course, a great random variation, but comparisons can be made between mean values of different groups.

Erythrocytes and plasma from ten normal adults and ten newborn babies were studied as well as erythrocytes from ten individuals with iron deficiency anemia. The mean values of k in these groups were compared to the mean value of k as obtained by analyzing eight samples of pure coproporphyrin III. As can be seen from Table 16, the mean values differed little from that of pure coproporphyrin; only in the last group (erythrocytes from sideropenic anemias) the mean k value was considerably higher. Attempts to study the porphyrin in the 0.24 N HCl extracts by paper chromatography were not successful.

Discussion

Earlier researchers have established that protoporphyrin is the main free porphyrin occurring in the human erythrocytes. Grotepass (1937) isolated the porphyrin and identified it by means of melting-point, and by spectral studies in different solvents, etc. Watson, Grinstein and Hawkinson (1944) made similar findings in erythrocytes from dogs and rabbits with stimulated erythropoiesis. The present findings confirm this. No traces of any 3-COOH-porphyrin have been found in erythrocytes from normal subjects or from patients with iron deficiency.

Watson (1950) noticed the presence of another porphyrin in erythrocytes from cases of pernicious anemia in remission; the porphyrin was extracted from ether by very dilute HCl. Schwartz and Wikoff (1952), studying mainly animals with stimulated erythropoiesis, isolated a corresponding porphyrin; its melting-point, spectrum and chromatographic behaviour indicated it to be identical with coproporphyrin. Sturgeon, Chen and Bergren (1958) report the chromatographic separation of the erythrocyte porphyrins. Coproporphyrin and uroporphyrin were found in the dilute acid extracts. However, the isolation of free uro- or coproporphyrin from normal erythrocytes has not been reported.

Chu and Chu (1959), studying copro-, uro- and 5, 6 and 7-COOH-porphyrins, found that, in general, an increase in the number of carboxyl groups was followed by a decrease of the "HCl-number" of an ethyl acetate/hydrochloric acid distribution. The 5-COOH-porphyrin was an exception, the HCl-number being the same as that of coproporphyrin.

In the present study, the "HCl-numbers" have been studied indirectly by observations of the porphyrin contents in the consecutive 0.24 N HCl-extracts. In all normal groups (plasma and erythrocytes from normal adults and from newborn babies) the observation suggested identity with coproporphyrin. This confirms the earlier observations, but it cannot be excluded that 5-COOH-porphyrin was present. Furthermore, small amounts of other porphyrins are probably not detected by this technique.

In patients with iron deficiency anemias, the observations suggested the presence of a porphyrin with higher HCl-number. Calculations revealed that this increase could not be explained by the admixture of protoporphyrin itself. However, in a series of ten determinations of pure protoporphyrin, the 0.24 N HCl extracts contained a fluorescing substance with still higher HCl-number. Thus the most probable explanation of the findings in iron

deficiency anemia is that the abundant protoporphyrin has formed degradation products which disturb the study of the 0.24 *N* HCl extracts.

4. Clinical application of the method

For the clinical use of the method, two additional questions had to be studied, viz. (1) is it necessary to wash the erythrocytes prior to the analysis and (2) must the leucocytes be removed?

Washing of the erythrocytes. In Chapter VIII, determinations of porphyrin in plasma are described. Protoporphyrin was found to be practically absent from plasma and thus the removal of plasma is of minor importance for the analysis of free erythrocyte protoporphyrin. In contrast, considerable amounts of a coproporphyrin-like pigment were present, corresponding to 0.4–3.2 μg coproporphyrin/100 ml plasma. It is therefore important to remove plasma before the analysis of ECP. After one centrifugation (1500 g, 30 minutes) with removal of supernatant plasma, the hematocrit of the sediment was 95 %. Considering the volume of "trapped plasma" of the hematocrit determination, the total amount of plasma left in the erythrocytes could be estimated to 10 % of the erythrocyte volume or less. Since the ratio between coproporphyrin-like pigments in plasma and free erythrocyte coproporphyrin generally is between 1:4 and 1:1, the omission of washing the erythrocytes can be calculated to increase the free erythrocyte coproporphyrin about 5 %. Considering the great random variation of the analysis and the risk of losses during the washings, this technique was thought justified.

Porphyrin in leucocytes. In order to exclude the possibility that important amounts of free porphyrins are present in the leucocytes, the following experiment was carried out. Whole blood from a normal male adult was centrifuged and the plasma and top cell layer removed. The remaining erythrocytes were resuspended in their own plasma but with the omission of the top cell layer. A leucocyte count revealed that 90 % of the leucocytes were removed by this procedure. After a second centrifugation, the concentration of free porphyrins in the erythrocytes was determined. The experiment was carried out in duplicate and the results were compared to that of two determinations performed on untreated samples of the same blood. The concentration of free copro- and protoporphyrin was essentially unchanged by the removal of the leucocytes.

Other methods used. Hematocrit determinations were made by a hematocrit centrifuge[1] after 5 minutes' centrifugation. During the early stages of the investigation, determinations were made by centrifuging 5 cm capillary tubes in an ordinary laboratory centrifuge at 1500 g during 30 minutes.

Hemoglobin determinations were made by the oxyhemoglobin or cyanmethemoglobin method, calibrated through the courtesy of the Department of Clinical Chemistry, University Hospital, Uppsala. Reticulocyte counts were performed after supravital staining during at least 20 minutes at room temperature using a 0.5 % saline solution of brilliant cresyl blue.

Standard statistical methods were em-

[1] International Micro Capillary Centrifuge, Model MB.

ployed. The significance of differences between mean values was judged by aid of the t-test.

5. Some general remarks on the method

Some inherent disadvantages and other characteristics of the method are pointed out below.

Because of the great random error, single determinations are able to reveal only rather considerable changes in the levels of the porphyrin. Thus, the statistical significance of a protoporphyrin difference smaller than 20 % or a coproporphyrin difference smaller than 40 % is low. This is true for porphyrin levels within normal limits; if the levels are increased, smaller percentual differences may be significant. On the other hand, differences found between subnormal values are almost always statistically insignificant. This is the case especially when coproporphyrin results are compared.

The isolation of the free protoporphyrin is far from quantitative. In this respect, the present method appears to be inferior to the method of Grinstein and Wintrobe (1948). The recovery of coproporphyrin is even less. Should corrections then be made for the low recoveries? It is generally assumed that the "free erythrocyte porphyrin" is actually free or present in some loosely bound form in contrast to the firmly combined protoporphyrin of the hemoglobin. Eriksen (1955) has found evidences of a protoporphyrin-globin complex. The protoporphyrin of this complex is included in the routine extraction and analysis of "free erythrocyte protoporphyrin". Possibly other porphyrin-protein complexes exist in the erythrocyte but to date no observation has been made supporting this. The corrected values obtained by the author's method are threfore supposed to represent all the non-heme (or -hemine) porphyrin in the erythrocytes. The magnitude of the corrections necessary to compensate for the losses during the analysis contribute to the inexactitude of the method. Comparisons between the results of different investigators cannot be made without due regard to the possibility of methodological differences.

In hematological investigations, studies of free erythrocyte proto- and coproporphyrin are not often necessary. In iron deficiency anemia, for instance (always accompanied by high levels of free erythrocyte protoporphyrin) the diagnosis is more easily made by aid of other laboratory tests. However, in cases which resembles the "sidero-achrestic" anemias (Heilmeyer 1959), studies of free porphyrins in the erythrocytes are important. In these cases and in other rare forms of hypochromic anemias, it would be of great interest to be able to identify the porphyrin, even in the isomeric form. In the present method, it is comparatively easy to identify protoporphyrin by its absorption peak in the Soret band; further evidence can be obtained by paper chromatography. In the present investigation, it has only been possible to characterize the free erythrocyte coproporphyrin by its distribution between ethyl acetate and dilute hydrochloric acid. The presence or absence of small amounts of porphyrins with 3, 5 or higher numbers of COOH-groups probably cannot be decided in this manner.

The hematoporphyrin which probably

may be formed from protoporphyrin during analysis disturbs the determination of coproporphyrin. When samples of erythrocytes with normal content of protoporphyrin are studied, the hematoporphyrin formation is negligible. But, when higher protoporphyrin levels are found, the results of coproporphyrin analyses must be judged cautiously.

The many steps of the analytical procedure are time-consuming. Attempts to shorten the procedure by reducing the number of extractions have not been successful. Reduction of the necessary volume of erythrocytes has also been considered, but this was found impossible since microcuvettes for the fluorometer were not available.

6. Comparison to earlier methods

In the present method, the recovery of added copro- and protoporphyrin is not quantitative. About 25% of the coproporphyrin and 20% of the protoporphyrin are lost during the analysis. Thus the results must be corrected. Higher recoveries can be obtained if a greater number of extractions are made. But this was found unsuitable for routine use. Also, the risk of losses, by the destruction of porphyrin, increases if the procedure becomes too time-consuming.

The correction values used for the lost porphyrins are only valid if the analyses are carried out exactly in the manner described. The volumes of the solvents and the number and time of extractions must always be the same. It is also important to avoid strong daylight in the laboratory. In the description of earlier procedures, it has for example been prescribed that extractions should be repeated until no red fluorescence is seen in ultraviolet light. However, in order to obtain constant recoveries in all determinations it must be safer to carry out a fixed number of extractions.

In earlier methods, corrections of the results have not been made for the losses of porphyrins. (Recovery experiments have been reported for the method of Grinstein and Watson 1948 only.) The present method should therefore give higher values than those obtained with earlier procedures.

The ratio between the protoporphyrin of hemoglobin and the free protoporphyrin in the erythrocyte is about 30,000:1. The heme moiety is split off from the hemoglobin during the first extraction and goes into the ethyl acetate/acetic acid mixture. Theoretically, it is not extracted from here by HCl. According to the author's experience, a contamination of the acid extract with hematin is inevitable. Even the final acid extracts seem to contain hematin. This absorbs light intensely in the 400 mμ-region. Thus the determination of protoporphyrin by its maximal light absorption in the Soret band will give erroneous results. Successful corrections can be made by a procedure suggested by Rimington and Sveinssen (1950) which includes measurements of the light absorption at 430 and 380 mμ. This method, adopted in the present investigation, has only recently been used by other authors (Rubino *et al.* 1958, Koskelo 1959, Prato *et al.* 1959).

The determination of coproporphyrin in erythrocytes is made fluorometrically and in the physical determination, no distinction can be made between copro- and

protoporphyrin. Therefore, to determine the coproporphyrin by itself, a separation of copro- and protoporphyrin by aid of their different solubilities is necessary prior to the fluorometrical determination. But the protoporphyrin concentration is much higher than the coproporphyrin concentration, and it is inevitable that traces of protoporphyrin are co-extracted in the coproporphyrin extracts. According to the method of Schwartz and Wikoff (1950), the protoporphyrin is removed by chloroform extraction. The present author has not found chloroform efficient. Instead, a procedure is used in which the amount of co-extracted protoporphyrin can be corrected for. The procedure includes six consecutive extractions with fluorometric determination of each extract. This may seem troublesome but two additional advantages are obtained.

Great amounts of porphyrin or admixture of hematin quench the fluorescence. If all extracts from one blood sample are combined, a quenching may not be observed and faulty results may be accepted. With the present method, quenching will always be recognized since in this case the regular decrease of fluorescence in the consecutive extracts does not occur. The second advantage is that the nature of the porphyrin is checked in the analysis. The measurements of the consecutive extracts allow a calculation of the porphyrin's distribution between ethyl acetate and hydrochloric acid. This is described further below.

Owing to the more efficient correction for the co-extracted protoporphyrin, the present method—other details being equal—should give lower coproporphyrin values than the method of Schwartz and Wikoff. However, the present method employs the more efficient extraction of 0.24 *N* HCl instead of 0.1 *N* HCl, which has the opposite effect.

The free protoporphyrin from normal human erythrocytes was identified by Grotepass (1937). He collected extracts from erythrocytes for three years and crystallized the protoporphyrin. Hitherto, the coproporphyrin has only been identified in extracts from erythrocytes of animals with stimulated erythropoiesis (Schwartz and Wikoff 1952).

In the present study, the protoporphyrin could be identified by the position of the Soret band peak and by paper chromatography. The presence of coproporphyrin in erythrocytes has gained support in this investigation by the distribution between ethyl acetate and dilute hydrochloric acid.

PART TWO

Clinical study

CHAPTER VI

Normal values in adults

The primary aim of the present investigation was to study the changes of ECP and EPP[1] during the first two years of extra-uterine life. For the following reason, it was considered advisable to study a number of normal adults as well. Methodological studies revealed that small variations in the analytical procedure may give considerable differences in the results. The findings of different authors are thus not necessarily comparable even if similar methods have been employed. It is equally uncertain if the present modification of the Schwartz and Wikoff (1952) method is comparable with the earlier methods. Thus basic values for adults are necessary for the evaluation of results obtained in infants and children.

Material. The series consisted of 20 males and 20 females, most of whom were doctors, students, nurses and other hospital and laboratory personnel. All were in apparently good health; no one had had infections during the preceding weeks. No one had donated blood during the preceding months. Most of the individuals were in the third or fourth decades of life. The blood samples were collected in the early afternoon and the subjects were not fasting. Hematocrit readings were not below 40 % in the males nor below 38 % in the females.

Results

Free erythrocyte coproporphyrin.

The results are shown in Table 17. The results of earlier investigations are also shown in this table. As can be seen, the values of ECP of 20 normal adult males ranged from 0.7 to 2.3 μg %, the mean value was 1.3 μg %. The corresponding values in females were: range 0.3–2.3 μg %, mean 1.2 μg %. No significant difference was found between males and females. As can be seen from the diagram in Fig. 13, the distribution of the values of males and females was somewhat different. In males, no value below 0.7 μg % was found, but in females, six values were below 0.5 μg %. The relation between the time of taking the blood sample and the menstrual cycle was not recorded.

Free erythrocyte protoporphyrin.

The values for EPP in 20 normal adult males varied between 16 and 52 μg %. The mean was 30 μg %. The corresponding values in females were: range 18–51 μg %; mean 37 μg %. In the diagram (Fig.13)

[1] *Abbreviations.* ECP = Free erythrocyte coproporphyrin. EPP = Free erythrocyte protoporphyrin. EP = Erythrocyte porphyrin (in earlier investigations, in which no difference has been made between copro- and protoporphyrin). The results are given in micrograms per 100 ml packed erythrocytes, abbreviated μg %.

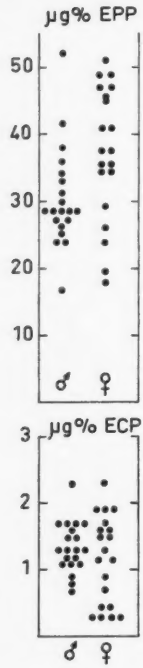

Fig. 13. Free erythrocyte copro- and protoporphyrin in healthy adults.

it may be observed that 19 of the males' values fell within 17 and 41 µg%. No abnormities were found in the individual with 52 µg% EPP, but studies of serum iron etc. were not performed. Hematocrit was 44%. The ECP was also high, 2.3 µg%. Duplicate determinations were made, the results of which were consistent.

The difference between the mean values of EPP found in males and females was found to be probably significant ($p < 0.05$).

Discussion

Free erythrocyte coproporphyrin. ECP values in normal adults have earlier been reported in four communications, the results of which are shown in Table 17. As can be seen, the present ECP results are similar to those found by Meduri, Notario and Casirola (1958). Prato, Mazza and Fiorina (1959), in a mixed material of males and females, found higher ECP, 0–3.5 µg%, on the average 1.5 µg%. The present results are higher than those found by Watson (1950) and by Krammer, Cartwright and Wintrobe (1954). In the studies

TABLE 17. *Present and earlier investigations of free copro- and protoporphyrin in healthy adults.*

Investigator	Year	No. of cases	ECP µg% Mean	ECP µg% S.D.	ECP µg% Range	EPP µg% Mean	EPP µg% S.D.	EPP µg% Range
Adult males								
Watson	1950	20	0.3	0.4	0 –1.0	29	4.5	24–42
Krammer *et al.*	1954	20	0.8	0.3	0.3–1.2	31	11.9	14–55
Meduri *et al.*	1958	15	1.1	0.7	0.3–2.5	30	10.7	18–49
Wranne	1960	20	1.3	0.4	0.7–2.3	30	7.5	16–52
Adult females								
Watson	1950	30	0.7	0.6	0 –2.0	42	5.9	32–52
Krammer *et al.*	1954	10	0.7	0.2	0.3–1.1	45	19.6	23–79
Meduri *et al.*	1958	15	1.3	0.6	0.5–2.8	31	8.1	21–47
Wranne	1960	20	1.2	0.7	0.3–2.3	37	10	18–51

of Watson and of Krammer *et al.*, the method described by Schwartz and Wikoff (1952) was used. It is believed, that the method used in the present investigation has given more efficient extraction and purification of the porphyrin. The higher coproporphyrin values now found are thus what could be expected from the methodological difference. In the report of Meduri *et al.*, the method for the determination of ECP is not clearly described. Prato *et al.* followed the just-mentioned method by Schwartz and Wikoff with two modifications: (1) plasma was not removed from the blood before analysis; (2) the final estimation of the coproporphyrin was made spectrophotometrically. According to the present author's findings, plasma of adults contains up to 1.5 μg% of a coproporphyrin-like porphyrin. Thus the high ECP results obtained by Prato *et al.* may be explained. It is also the present author's experience that spectrophotometry is inferior to fluorometry for the determination of ECP. Thus the relatively greater scattering of the ECP values found by Prato *et al.* may be explained.

Free erythrocyte protoporphyrin. The results of the determinations of EPP in males are almost identical in the investigations of Watson (1950), Krammer *et al.* (1954), Meduri *et al.* (1958) and in the present investigation (cf Table 17). In females, the results of these investigations are more varying. The average EPP values range from 31 to 45 μg%. The highest mean value was found in the study of Krammer *et al.* In their material, the range was remarkably great, the highest value found in one individual being 79 μg%. The possible causes of high EPP values will be discussed later.

The finding of similar mean values of EPP in the investigations made by aid of the Schwartz and Wikoff technique and by the author's method is remarkable. According to the methodological studies, the present modification of the Schwartz and Wikoff method is expected to give better extraction and hence higher EPP values. This should be particularly pronounced since corrections were made for the non-quantitative recovery of the present method. On the other hand, other differences in the methods may have been important; e.g., the present use of the correction by Rimington and Sveinssen which tends to decrease the results of EPP determinations.

Since the free erythrocyte coproporphyrin is small compared to the free erythrocyte protoporphyrin, comparisons can also be made with the earlier investigations of undifferentiated free porphyrin (Table 18). These investigations are in most cases performed according to the methods of Grinstein and Watson (1943) or Grinstein and Wintrobe (1948). These methods are essentially the same, the latter being a micromodification of the former. The determination of the protoporphyrin in the final extracts of the Grinstein and Watson method (1943) is generally performed with a photoelectric colorimeter, but some workers have made modifications: Ward and Mason (1950) use a fluorometer, Sturgeon (1954) a spectrophotometer. In the method by Grinstein and Wintrobe (1948) a spectrophotometer is always used. Here the recovery of added protoporphyrin was about 90%. The results were not corrected for the 10% loss. In most investigations, the results are calculated from the maximal light absorption

TABLE 18. *Earlier investigations of free erythrocyte porphyrin compared to the present results.*

Investigator	Year	Males			Females		
		Number of cases	Mean μg%	Range μg%	Number of cases	Mean μg%	Range μg%
Watson *et al.*	1944	8	26	20–36	4	38	31– 46
Cartwright *et al.*	1948	33	32	13–79	33	39	16–140
Bénard *et al.*	1949	8	18	9–27	4	18	14– 24
Ward and Mason	1950	40	44	13–92	37	42	17–139
Ventura and Klopper	1951				25	31	18– 50
Holly	1953				42	43	23– 67
Ventura and Meduri	1954	20	33	17–48	25	31	18– 50
Sturgeon	1954	34	23	10–50			
Sturgeon	1959				20	28	—[a]
Koskelo	1959	23	17	8–32	6	18	11– 21
Wranne[b]	1960	20	30	16–52	20	37	18– 51

[a] Selected material: only nulliparae. Range not given. S.D. ± 13 μg%.
[b] Free erythrocyte protoporphyrin.

in the Soret band. Only Koskelo (1959) uses the correction proposed by Rimington and Sveinssen (1950). In Table 18 the results of ten earlier investigations of EP are shown. As can be seen, the results are most varying, the mean EP values in male ranging between 17 and 44 μg%. The corresponding range of mean EP values of females is 18–43 μg%. The great variation between the results can be due to differences in the performance of the analytical procedure, but it may also be an effect of real difference between the groups of individuals studied. Iron deficiency and infections are known to increase the EP values (Cartwright *et al.* 1946, 1948) and the presence of infections or iron deficiency in a so-called normal material is perhaps conceivable. In the study of Holly (1953) the EP of 42 healthy, non-pregnant females was determined. The range was found to be 23–67 μg%. To four of these women, who showed EP values above 50 μg%, iron was administered. In each case, after treatment, the EP values was found to be below 50 μg% indicating a latent iron deficiency.

In the study by Cartwright, Huguley, Ashenbrucker, Fay and Wintrobe (1948) 33 normal males and 33 normal females were investigated. The mean EP in males was 32 μg%, and in females 39 μg%. The EP values ranged from 13 to 140 μg%. However, only three of the men and three of the women had EP values exceeding 60 μg%. It is tempting to postulate that some abnormal condition was present in these cases, but they are not separately discussed by these authors. In the study of Ward and Mason (1950), a few very high values were also recorded in the normal group, the highest being 139 μg%. These authors suggest that elevated EP values may be caused by mild chemical toxicity, in some cases including the use of alcohol.

On the other hand, two earlier investigations have given remarkably low values of EP, the mean value being below 20 μg%. In the investigation of Bénard, Gajdos and Canivet (1949), the number of in-

vestigated individuals is small: 8 males and 4 females. The statistical error of the mean is consequently great and the low mean values are perhaps explained by the random variation. Low values have also been reported by Koskelo (1959). These may be due to the fact that Koskelo used the Rimington–Sveinssen correction (p. 14), which often gives lower EP values.

The remaining reports of EP have given results which are in agreement with the present findings. Watson, Grinstein and Hawkinson (1944), Ventura and Klopper (1951), Ventura and Meduri (1954 a), Sturgeon (1954 and 1959) have in all investigated 62 males and 74 females. In males, the EP values range from 10 to 50 μg %, averaging 27 μg %. In females, the range is 18–50 μg %, averaging 31 μg %. These investigations were carried out by aid of the method of Grinstein and Watson (1943) or that of Grinstein and Wintrobe (1948). In the latter, the recovery of added protoporphyrin was about 90 % and it is probable that the method of Grinstein and Watson gives similar recovery. Thus the results should be multiplied by 1/0.9 in order to be comparable with the present results. After this correction, the mean EP in males is 30 μg % and the mean EP in females 34 μg %.

It seems justified to conclude that EPP determinations by the present method give results consistent with most of the earlier investigations of EP.

Individual variations of ECP and EPP.

Determinations of ECP and EPP were done at approximately the same time on different days during a period of two months in a healthy adult male. The ECP values were: 0.8, 0.8, 0.7, 0.7, 1.1 and 0.7 μg %. The EPP values were: 27.0, 35.4, 30.7, 26.6, 34.0 and 28.5 μg %. In another healthy adult male, determinations were made for a period of two years; i.e., during the major part of the time for this investigation. The ECP values were: 1.3, 1.1, 1.3, 1.3, 1.2 and 1.2 μg %. The EPP values were: 23.7, 29.5, 27.0, 28.7, 26.2 and 31.3 μg %.

The variations of ECP and EPP in the same individual appear to be smaller than those found between individuals. The finding of small variations of ECP and EPP within individuals is in accordance with earlier investigations. Cartwright *et al.* (1948), studying males as well as females, state that the variation of EP is not marked and that no correlation to the menstrual cycle can be observed. Ward and Mason (1950) found only small variations of EP. Ventura and Meduri (1954 a) could not establish any variations of EP during the course of the day, nor during the course of a year. Meduri *et al.* (1958), studying both EPP and ECP, found no significant variation during the menstrual cycle.

The present findings also indicate, that no gross systematic error occurred in the investigation.

CHAPTER VII

Normal values from birth to the age of two years

Material

Umbilical cord blood was obtained from twenty newborn babies delivered at the Obstetric Clinic in Uppsala. All deliveries were normal and occurred between 13 days before and 17 days after the expected time. There was no cases of asphyxia; birth weights ranged from 2500–4000 g; all mothers were healthy; hemoglobin levels of the mothers were not below 10 g/100 ml; there were no Rh-incompatibilities between mother and child and no child was abnormally icteric during the neonatal period.

Forty-one healthy infants and children from 9 days to 19 months old were also examined. Most of these were children nursed at the Pediatric Clinic in Uppsala for various reasons. A few were from two nurseries in Uppsala and Linköping. All infants were examined physically and care was taken to avoid individuals who were infected or had been infected during the previous weeks. However, it was inevitable, that the infants from the nurseries had had minor upper respiratory infections during the weeks prior to the investigation. These infants are therefore included in a special group. All infants and children had hemoglobin and hematocrit levels within the limits established by Albritton (1952). All samples consisted of venous blood taken in the fasting state between 7 and 9 o'clock in the morning. No distinction was made between boys and girls.

Results

The present results are shown and compared to earlier results in Tables 19 and 21. The individual values are shown in a diagram, Fig. 14.

Cord blood. ECP in cord blood varied between 1.1 and 7.2 μg% and EPP between 32 and 135 μg%. No correlation between the birth-weight or gestation time and porphyrin levels could be established. There was no distinct correlation between ECP and EPP variation, although the highest ECP value, 7.2 μg% was accompanied by the second highest EPP, 93 μg% and similarly the highest EPP, 135 μg% corresponded to the second highest ECP, 6.0 μg%. These children showed no abnormalities during the neonatal period. Labor had not been difficult. No anemia was present. They were physically normal at examination, and special hematological investigation was not performed.

The mean value of EPP was 54 μg% and of ECP 2.8 μg% and the standard deviations of the observations ± 25 μg% and ± 1.6 μg% respectively. If the two highest values of ECP and EPP are disregarded.

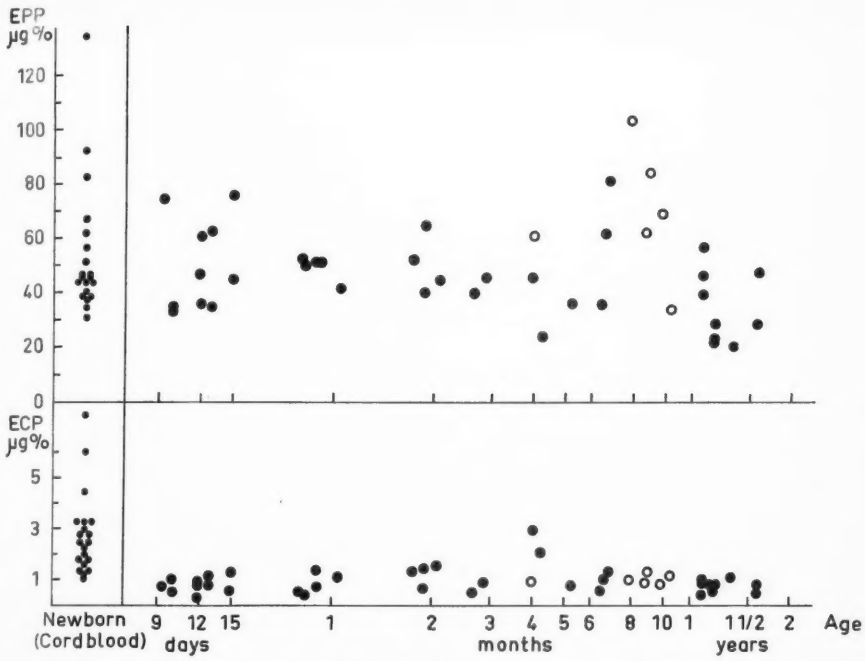

Fig. 14. Free erythrocyte copro- and protoporphyrin in healthy infants from birth to the age of two years. ○ = infants from nurseries.

the frequency distribution curves appeared to be approximately symmetrical. The medians were 48 and 2.5 µg %, respectively.

Infants and children 9 days–19 months old

The ECP level fell from a maximum level at birth to a very low level within the first two weeks. The difference between the level at birth and at the age of 9–15 days was statistically highly significant ($p<0.001$). ECP levels remained normal or slightly low, compared to adults, during the rest of the investigated period. One ECP value was found astonishingly high, 2.9 µg % in a four month old girl, admitted to the hospital for a diaper rash of moderate intensity. However, no abnormalities could be found in the child and an error of analysis seems not improbable. Unfortunately, a reticulocyte count was not performed in this case.

The mean EPP of infants 9–15 days old was found to be 51 µg %, which is insignificantly lower than the mean value found in cord blood. In the age-group 15 days to 4 months, no certain trend towards lower values was found, the average being 49 µg %.[1] Infants 4 months to 12 months of age showed widely scattered EPP values, the lowest being 25 µg %, the highest 125 µg %. It should be noted that

[1] The mean EPP of infants 9 days–4 months old was significantly higher than the mean EPP of adult males as well as that of adult females ($p<0.001$).

TABLE 19. *Free erythrocyte copro- and protoporphyrin in cord blood.*

Author	Number of cases	EPP, μg%		ECP, μg%	
		Mean	Range	Mean	Range
Schwartz and Wikoff 1952[a]	2	—	8.1; 5.3	—	178; 69
Hsia and Page 1954[a]	6	1.5	0.6– 2.8	125	63–203
Prato, Mazza and Fiorina 1959[b]	10	7.9	4.4–12.6	72	46–116
Wranne 1960	20	2.8	1.1–7.2	54	32–135

Methods: [a] Schwartz and Wikoff 1952; [b] Schwartz and Wikoff 1952, but coproporphyrin estimated spectrophotometrically. Plasma included.

among the four children having EPP values exceeding 70 μg%, three were inmates of nurseries.

The last group of children studied, aged 1–2 years, showed lower mean EPP level than the younger infants. The mean EPP of the former was found to be 32 μg%, only insignificantly higher than that of normal male adults.

Discussion

Comparison to earlier findings

Free erythrocyte coproporphyrin in cord blood has been studied by Schwartz and Wikoff (two cases, 1952), by Hsia and Page (six cases, 1954) and by Prato, Mazza and Fiorina (ten cases, 1959). The results of these investigations are compared to the present results in Table 19. Compared to the present findings, the two cases studied by Schwartz and Wikoff (1952) showed unusually high values. In contrast, the results of Hsia and Page gave lower mean ECP values than the present study. No normal material of adults were studied by these authors. One possible explanation of the divergent findings is that their method for ECP determination has given lower results than the present modification of the Schwartz and Wikoff method.

The method for ECP determination used by Prato, Mazza and Fiorina (1959) has been discussed earlier (p. 49). ECP values obtained by this method are probably too high owing to the inclusion of plasma in the analyses. However, their mean ECP value of cord blood is almost three times as high as the present. This difference cannot be sufficiently explained by the inclusion of plasma. The description of their technique is not detailed enough to allow a discussion of other causes of the difference.

Free erythrocyte protoporphyrin in cord blood has been studied by the authors just mentioned (Schwartz and Wikoff, 1952, Hsia and Page, 1954, Prato *et al.* 1959). Their results are also shown in Table 19. However, since the ECP is small compared to the EPP, comparison can also be made with the results of earlier investigations of EP (Table 20). As can be seen from the tables, the mean EPP (or EP) values found by the earlier authors are most varying. The range of the mean values found is 13 to 125 μg%. It is obvious that this great variation to a considerable degree must be due to methodological differences in the different investigations. In an attempt to compensate for methodological differences, the results of EPP (or EP) determinations

Correction

Lars Wranne: *Free erythrocyte copro- and protoporphyrin.*
Acta Pædiatrica, Vol. 49, Suppl. 124, p. 54, Table 19.

Instead of:

Author	Number of cases	EPP, μg %		ECP, μg %	
		Mean	Range	Mean	Range

Read:

Author	Number of cases	ECP, ug %		EPP, ug %	
		Mean	Range	Mean	Range

in cord blood were compared to the same author's results of determinations of erythrocytes from normal male adults. Such comparisons could be made in the investigations of Ventura and Meduri (1954a), Sturgeon (1954 and 1959), Prato, Mazza and Fiorina (1959) and in the present investigation. With the exception of Ventura and Meduri, all these investigators found that the mean EPP (or EP) of cord blood is about twice as high as that of normal male adults. In contrast, the study of Ventura and Meduri showed that in twelve newborn babies the mean EP was lower (29 μg %) than that of normal male adults (33 μg %). It has not been possible to find any explanation of this discrepancy. In the investigations in which the highest and lowest mean EPP (or EP) values were found, no adults have been included. In the study of Carletti (1956) the EP was studied in cord blood from thirty-two newborn babies. The range was found to be 3.4 –31 μg % and the mean value 12.8 μg %. It seems most probable that some profound difference in the performance of the determination has existed between the study of Carletti and other investigations. — The highest mean EPP value is reported by Hsia and Page (1954): 125 μg %. Six newborn babies were included. Since no adults were studied it is impossible to judge the significance of this result. Sturgeon (1954) has studied 41 infants, ½–11 days old. The mean EP found in cord blood, 55 μg %, was found to be decreased about 10 μg % during the first two days of life. After that, it remained almost unchanged during the period investigated. This is in accordance with the present results. The age-group between ½–4 months does not seem to have been investigated earlier. A great number

TABLE 20. *Earlier investigations of free erythrocyte porphyrin in cord blood.*

Author	Number of cases	Mean μg %	S.D. μg %
Ventura and Meduri 1954[a]	12	29	9.7
Carletti 1956[a]	32	13	4.9
Sturgeon 1954[b]	22	55	16.9
Sturgeon 1959[b]	129	42	14.3

Methods: [a] Grinstein and Wintrobe 1948;
[b] Grinstein and Watson 1943.

of infants, 4 months to two years of age, have been investigated by Sturgeon (1954, 1958 and 1959). In the infants studied in 1954, mean EP values increased from the age of four months to a maximum of 160 μg % at the age of two years. The infants came from an underprivileged social group. Iron deficiency was probably common since, e.g., at twelve months' age the mean hemoglobin concentration was only 9.9 g/100 ml and the mean erythrocyte hemoglobin concentration 28.8 %. In another study, Sturgeon (1959) investigated infants and children from well-to-do families. As can be seen in Table 21 much lower EP values were found, essentially equal to the present findings. These infants were given a relatively advanced feeding routine, similar to that given to the infants in the present study. The effect of parenteral iron administration was also studied by Sturgeon (1958 and 1959). The injection of 250 mg iron at 9 months of age was followed by decreased EP values upon examination at 12 and 18 months' age.

Physiological Aspects

During the first year of extra-uterine life, important hematological events occur. At birth, the hemoglobin content of blood

TABLE 21. *Present results of ECP and EPP determinations compared to the EP results of Sturgeon (1954 and 1959).*

Age group	Sturgeon 1954		Sturgeon 1959		Age group	Wranne 1960		
	No. of cases	EP μg %	No. of cases	EP μg %		No. of cases	EPP μg %	ECP μg %
Umbilical cord blood	22	55	129	42	Umbilical cord blood	20	54	2.8
2–11 days	31	45			9–15 days	10	51	0.8
					15 days–4 months	11	49	0.9
6 months		46	96	42	4 months–1 year	6[a]	48	1.5
12 months		104	91	35				
18 months		81	90	31	1–2 years	8	32	0.8

[a] Infants from nurseries excluded.

is high, serum iron elevated (Vahlquist 1941) and the total iron-binding capacity of serum slightly depressed (Smith *et al.* 1952, Hagberg 1953a). These findings as well as studies of the iron depots (Widdowson and Spray 1951) indicate that the depots are being built up. At birth, there are evidences of an accelerated erythropoiesis with reticulocytosis and extramedullary hematopoiesis. The high hemoglobin level also indicates that the erythropoiesis has been intense during the latter part of the fetal life. During the first few days of extra-uterine life, all signs of increased erythropoiesis disappear (Langley 1951, Seip 1955); during the following two months, decreased blood-formation and increased iron-storage occur (McCance and Widdowson 1951). During the remaining part of the first half-year, there is a successive return to full hematopoietic activity and simultaneously a successive decrease of serum iron and increase of the total iron binding capacity (Smith *et al.* 1952, Hagberg 1953a). These findings indicate that the iron depots are gradually emptied during this period. From the age of one or two years, normal adult conditions are gradually achieved.

The factors which cause the high hemoglobin level in newborn babies are not sufficiently known. Probably the most important factor is that the fetus *in utero* is living under a reduced oxygen tension. Studies of pO_2 by Sjöstedt, Rooth and Caligara in amniotic fluid (1958) and in the intervillous space of the placenta (1960) have indicated that pO_2 in the umbilical vein *in utero* is about 40 mm Hg and pO_2 in the tissues of the fetus probably is as low as 10 mm Hg. It thus seems justified to compare the newborn baby's high hemoglobin level with the polycythemia of high altitudes.

Can a relationship between the changes of free erythrocyte copro- and protoporphyrin from delivery to the age of two years and the physiological hematological processes just mentioned be found? Since it has been noted that several conditions with increased hemoglobin synthesis are followed by increased ECP (Watson 1950), the high values found in cord blood probably reflect the increased erythropoiesis. The rapid decrease in ECP, reaching normal or low levels by the second week of life, is also in accordance with the rapid disappearance of other signs of increased

erythropoiesis. However, other factors altering ECP cannot be excluded. The reduced oxygen tension of the fetal tissue may directly increase the ECP since studies of Falk, Porra, Brown, Moss and Larmine (1959) have established a direct effect of pO_2 variation on the biosynthesis of porphyrins and heme in chicken blood. The extramedullary erythropoiesis in the fetus may perhaps give erythrocytes with higher ECP content. Finally, the formation of hemoglobin F could be connected with high ECP level. Nevertheless, the rapid decrease of ECP after the delivery is not accompanied by a corresponding decrease in the formation of hemoglobin F. The formation of the latter has been found to continue during the first month of life (Vest 1959, Garby *et al.*, pers. commun.). After the first week of life, erythropoiesis seems to be depressed during the following two months. The low ECP values found are thus what could be expected. The ECP values remain normal or slightly low during the rest of the investigated period. This is in accord with observations that reticulocytosis does not normally occur during this age. It should be noted, however, that the significance of subnormal ECP values obtained by the present method is low.

The mean EPP in cord blood is doubled compared to the normal level for adult males according to the present investigations as well as to those of Sturgeon (1954 and 1959) and Prato, Mazza and Fiorina (1959). The most common causes of increased EPP levels, infections and iron deficiency, cannot have any influence in the newborn babies studied, since only healthy infants were included and since many investigations have established that no signs of iron-deficiency can be detected in newborn babies (for references, see above). The nutrition of the mother seems also to be of minor importance since in the study by Sturgeon (1959), the EP of the newborn child was not influenced by iron supplement to the pregnant mother. In the following, three additional causes of increased EPP will be discussed; viz., the accelerated erythropoiesis, the hypoxia of the fetus and the F-hemoglobin formation.

The accelerated erythropoiesis of the newborn baby may to some extent be the cause of the increased EPP in cord blood. In four cases of hemolytic anemia with reticulocytosis from 12–30 %, Watson (1950) found increased ECP, 30–50 μg %. The EPP levels, however, were only moderately increased—in three cases 60–65 μg %. Thus it seems doubtful that the increased erythropoiesis should be the only factor giving increased EPP in newborn babies.

The hypoxia of the fetus during intrauterine life may be an important factor. Interesting comparisons can be made with other conditions with hypoxia or impaired cardiopulmonary function. Six individuals living at high altitudes (15,000 feet) have been studied by Reynafarje, Lozano and Valdivieso (1959). The EP was found to be increased, averaging 105 μg %. The high EP could not be explained by other factors such as iron deficiency. After descent to sea level, the mean EP fell to 60 μg % after about two weeks and to about 55 μg % after one month.

The effect of short-time impairment of the pulmonary function has been studied by Bariéty, Gajdos, Török and Gimbert (1958). Air was insufflated in the mediastinum for diagnostic purposes in seven

patients with initially normal EP values. The insufflation was known to cause a transitory depression of pulmonary function as measured by the vital capacity, the maximum breathing capacity and the timed vital capacity (Bariéty, Coury and Gimbert 1958). After 72 hours, all tests were normalized. No clinical symptoms such as dyspnea or cyanosis occurred. An increase of EP levels was found during the week after the insufflation. The maximal values exceeded the original values by 58 to 206 %. On the eighth day, EP values were normalized. In three cases, hemoglobin concentration, red cell count and serum iron were also studied. No alterations were found. The authors conclude that the increase of EP was due to an increased synthesis of hemoglobin. The latter increase was thought to depend on the depressed respiratory function following insufflation. However, studies of ECP, reticulocytes or arterial pO_2 were not carried out.

In ten cases of congenital heart disease with secondary polycythemia, Koskelo (1959) found increased EP values in six of the cases. This was thought to be due to a "relative lack of iron available for the greatly increased hemoglobin synthesis".

These studies indicate that the EP levels are dependent on the tissue oxygen tension. It is not known whether the pO_2 affects the porphyrin and heme synthesis directly or if the increased EP is a secondary effect of an increased erythropoietic activity or a "relative lack of available iron". The studies of Falk *et al.* (1959) mentioned above indicate that a direct effect on the porphyrin synthesis is not improbable.

The formation of hemoglobin F could be connected with the increase of EPP. Studies of ten cases of thalassemia major (Sturgeon, Chen and Bergren 1958) did not, however, reveal any increase of EPP, nor did Watson's study (1946) of one case of this disease. Although these cases were not described in detail, it can be supposed that a considerable hemoglobin F formation occurred in many of them. Accordingly, hemoglobin F probably is of little or no importance for the actual changes of EPP.

During the first four months of life, the EPP has been found to be nearly constant, averaging 50 μg %. Compared to the mean EPP of normal adult males, this value is clearly elevated. Since iron deficiency seldom occurs before the age of four months and since the investigated infants had not been noticeably infected this EPP value is astonishing. In adults with conditions of increased EPP, decreasing values are usually seen within a few weeks or a month after the elimination of the causal factor. This was the case in the mountain inhabitants studied by Reynafarje *et al.* and in the patients investigated by Bariéty *et al.* However, in the latter study, it is uncertain how much of the change was due to ECP. The present author's study of iron deficient individuals treated with intravenous iron therapy revealed that EPP decrease generally was evident within a week.

Beginning at the age of three to four months and lasting up to one year, the EPP values have been found to be most varying. This is consistent with earlier findings. Since low EP values could be obtained by Sturgeon (1958 and 1959) by the parenteral administration of iron, the great variation seems to be an effect of the

well-known relationship between iron deficiency and increased EPP (or EP) values. However, an EPP-increasing effect of repeated infections cannot be excluded. In the present investigation, the relationship between the EPP and iron deficiency could not be studied.[1]

Children aged 1–2 years were found to have EPP levels only slightly higher than those found in normal adult males. This result is thought to indicate that no important iron deficiency was present among these children.

Children over 2 years of age were not studied since the investigations of children 2–15 years old made by Sturgeon (1954), Hsia and Page (1954), Ventura and Meduri (1954a) and by Carletti and Camerini (1958) have failed to establish any relationship between age and EPP. Moreover, repeated studies of iron metabolism have shown that no marked physiological changes occur before puberty (Vahlquist 1941, Smith *et al.* 1952, Hagberg 1953a and others).

[1] Owing to a technical mishap, all plasma samples intended for the determination of serum iron and iron binding capacity were lost during the analysis.

CHAPTER VIII

Porphyrin in plasma

The presence of porphyrin in plasma or serum has been much disputed for a long time. Schumm (1916 and 1939) never could find porphyrin in sera from normal individuals while Fischer and Zerweck (1924) reported the constant presence of a porphyrin similar to coproporphyrin. Van den Bergh, Grotepass and Revers (1932), studying more than 350 normal and pathological sera, found signs of porphyrin only in cases of obstructive jaundice and congenital porphyria. Similar findings were reported by Vigliani and Sano (1940). Vigliani and Angeleri (1936), Vigliani and Waldenström (1937) and Kench, Gillam and Lane (1942) found porphyrin, probably protoporphyrin, in serum from patients with lead poisoning. On the other hand, de Langen (1949) reports the presence of coproporphyrin in serum from plumbism patients. The latter author found traces of porphyrin, probably coproporphyrin, in normal sera also. Ward and Mason (1950), studying EP, also investigated porphyrin in the plasma. In five normal subjects, levels between 0.2–0.5 μg/100 ml were found, determined by fluorescence and calculated as protoporphyrin. In six cases of obstructive jaundice, higher values were found, up to 5.6 μg/100 ml; in cases of porphyria up to 8.4 μg/100 ml. No attempts to characterize the porphyrin were made. The constant finding of coproporphyrin in the urine of normal adults (Zieve, Hill, Schwartz and Watson, 1953) makes probable that coproporphyrin normally occurs in plasma.

Newborn babies and fetuses were studied by Fikentscher (1935), using a spectrographic technique. One to three μg/100 ml serum were found in the newborn contrasting to the absence of porphyrin in sera from the mothers. The spectrum of the plasma porphyrin closely resembled that of pure coproporphyrin I and III. The free erythrocyte proto- and coproporphyrin were not studied.

Results

Samples of plasma from twenty-seven normal individuals were examined. Sixteen were newborn babies and the blood was obtained from the cord. The rest were healthy adults. The samples were analyzed according to the author's method for determination of free erythrocyte copro- and protoporphyrin and, as a rule, 5 ml plasma was used. In some cases, however, only 3 or 4 ml were available. No significant amount of protoporphyrin-like pigment was found, but in the final 0.24 *N* HCl fractions a coproporphyrin-like pigment regularly appeared, although in small quantities. The distribution of this pigment between HCl and ethyl acetate

TABLE 22. *Plasma porphyrin in normal individuals.*[a]

	Number of cases	Mean μg/100 ml	Range μg/100 ml	S.D. μg/100 ml
Newborn babies	16	1.5	0.7–3.2	0.7
Adults	11	0.8	0.4–1.5	0.3

[a] The results are calculated as coproporphyrin.

was studied as described in Chapter V and found to be very similar to that of pure coproporphyrin and that of coproporphyrin from erythrocytes. Attempts at paper chromatography were not successful.

As can be seen from Table 22 and Fig. 15 the samples of plasma from adults contained 0.4–1.5 μg % of a coproporphyrin-like pigment. In newborns, the corresponding range was 0.7–3.2 μg %. In the figure, the individual values are presented together with the results of simultaneous analyses of free erythrocyte coproporphyrin. No significant correlation between plasma porphyrin and ECP could be found in the samples from adults or in the samples from newborn babies. In 22 of the 27 cases, the ratio between plasma porphyrin and erythrocyte coproporphyrin varied from 0.25:1 to 1:1.

In newborns, the mean plasma porphyrin was found to be 1.5 μg while in adults it was 0.8 μg/100 ml. The difference between the mean values found in normal adults and in newborn babies was found to be significant ($p = 0.01$).

In ten cases, double determinations were performed, and the error of the analysis calculated. The mean value of these determinations was 1.2 μg %, the standard error of a single determination was 0.25 μg %.

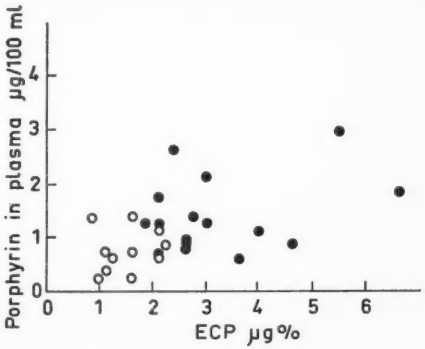

Fig. 15. Free erythrocyte coproporphyrin compared to porphyrin in plasma in adults (○) and in newborn infants (●). Plasma porphyrin calculated as coproporphyrin.

This result is in agreement with the corresponding error found in the analysis of free erythrocyte coproporphyrin.

Discussion

The nature of the plasma porphyrin. Before entering on a discussion of the identity of the plasma porphyrin, some attention must be directed to the question as to whether the observed substance really is a porphyrin at all. The presence of fluorescent substances in the final hydrochloric acid extracts after the numerous distributions between acid and organic solvents strongly indicate the presence of a porphyrin. It cannot be a product of impurities in the reagents as suitable corrections for blank values were employed (p. 33). Finally, the results of earlier investigators support the opinion that a real porphyrin exists in plasma.

In regard to the identity of the porphyrin in plasma, coproporphyrin seems to be the most probable; but this conclusion is founded only on studies of the distribu-

tion properties of the porphyrin. Thus hematoporphyrin could easily simulate coproporphyrin, but the former porphyrin has never been shown to occur normally in animals and its presence in plasma would seem, therefore, unlikely. The simultaneous presence of other porphyrins, similar to coproporphyrin, and probably present in the normal metabolism (e.g. the 3-COOH-porphyrin of Granick and Mauzerall, 1958b and 5-, 6- and 7-COOH-porphyrins, Granick and Mauzerall 1958a or even uroporphyrin) cannot be excluded. But in view of the present findings and the findings of earlier workers, it seems justified to assume that most of the plasma porphyrin is coproporphyrin.

The physiological importance of the plasma porphyrin is still unclear, since the origin as well as the elimination of plasma porphyrin are largely unknown. The presence of increased amounts of plasma coproporphyrin in a case of erythropoietic porphyria (Schmid, Schwartz and Watson 1954) indicates that some plasma porphyrin may derive from the hemoglobin synthesis. The probable enzymatic defect in this disease is an excess production of copro- and uroporphyrin of the I isomer, which, even normally, cannot be utilized for the synthesis of protoporphyrin IX and heme. In normal subjects, only small amounts of uro- and coproporphyrin type I are formed but are probably one source of the plasma porphyrin.

The free erythrocyte coproporphyrin may also contribute to the plasma porphyrin. Schwartz and Wikoff (1952), studying the isomeric composition of the free erythrocyte coproporphyrin in bled animals, found about 10 % type I and 90 % type III coproporphyrin. Since the former cannot be utilized and since coproporphyrin is most abundant in reticulocytes, there is a possibility that coproporphyrin I is passing out from the maturing erythrocytes into the plasma. All coproporphyrin type III may not necessarily be utilized for the synthesis of heme and protoporphyrin; it may also pass from the erythrocytes. A direct release of coproporphyrin from the bone marrow is also conceivable. Finally, the plasma porphyrin level is in some way related to liver function. In liver disease, increased amounts of porphyrin have been found by Ward and Mason (1950) and others, and porphyrin is also excreted in increased amounts in the urine (Watson, Capps, Rappaport and Hawkinson 1949). In the urine, the porphyrin was found chiefly to consist of coproporphyrin type I. The most probable explanation of these findings is that coproporphyrin normally is eliminated via the liver.

The findings of increased plasma prophyrin levels in newborn babies might be dependent on two factors: (1) the increased erythropoiesis during fetal life and at birth; (2) a deficient excretion by the liver. However, a certain elimination seems to occur since coproporphyrin has been found in meconium from newborn babies (Nicholas and Rimington 1951). According to Prato *et al.* (1959), the coproporphyrin is chiefly of type I.

CHAPTER IX

Changes of free erythrocyte copro- and protoporphyrin during iron treatment of iron deficiency anemia

The constantly high EPP of infants up to the age of four months has been found difficult to explain. In order to be able to compare with another condition with increased EPP, a number of patients with iron deficiency anemia were studied before and during intravenous iron treatment.

Studies of ECP and EPP during the specific treatment of iron deficiency anemia have not been reported earlier as far as can be ascertained. However, in three investigations, the changes of EP during iron therapy have been studied. Watson (1944) and Cartwright *et al.* (1946) followed the changes during oral iron administration; Pagliardi *et al.* (1959) studied the EP during intravenous iron therapy.

Material

Four women were studied. The diagnosis of iron deficiency anemia was based on the following hematological findings: anemia, low mean erythrocyte hemoglobin concentration, low serum iron, increased total iron-binding capacity of the serum. There were also "epithelial" symptoms in cases 1 and 2. A history of deficient nutrition was obtained in all cases but no. 4.[1] In Table 23, the hematological findings are summarized.

Two healthy women, 23 and 29 years old, were also studied. The criteria for their hematological normalcy were: hemoglobin concentration 13.0 and 13.4 g/100 ml, mean erythrocyte hemoglobin concentration 31.5 and 32.0 %, serum iron 171 and 114 μg/100 ml. No epithelial symptoms of iron deficiency were present. There was no history of increased menstrual blood loss.

Saccharated iron oxide containing 20 mg iron per ml was administered intravenously. At the first injection, 20–40 mg iron was generally given as a test dose. Since no untoward reactions occurred, the treatment was continued with injections of 100 mg iron every day or every other day. The total amount of iron given to the patients was 0.5–1.0 g. The healthy women were given 140 mg iron in all.

Results and Discussion

All patients responded to the iron administration by increased hemoglobin values. The average increase for a successful iron treatment established by Wintrobe (1956), a daily hemoglobin increase of

[1] In case 3, the iron deficiency was accompanied by pica, chiefly for match-tips. This habit was given up more than two weeks before the present study.

TABLE 23. *Initial hematological values in the patients.*

Case	Record no.[a]	Age	Hemoglobin g/100 ml	Hemato-crit %	Reticu-locytes %	MCHC %	S.I.[b] µg/100 ml	T.I.B.C.[b] µg/100 ml
1. E.H.	M 2340/59	16	6.8	27	2.4	24	43	392
2. H.E.	M 2593/59	76	7.6	28.5[c]	3.4	27	39	416
3. A.S.	P 184/60	14	6.6	26	3.0	25	8	413
4. M.S.M	O 391210	20	8.0	32[c]	—	25	30	435

[a] M: Medical Clinic, MO: Medical Clinic, out-patient department, P: Pediatric Clinic.
[b] Determinations of serum iron (S.I.) and total iron binding capacity (T.I.B.C.) were carried out in the Department of Clinical Chemistry of Uppsala.
[c] Venous blood.

0.17 g per 100 ml, was exceeded in all cases.

Initial values of EPP. The EPP was high in all patients before the therapy was started. The values found, 186–513 µg %, are consistent with those of Watson (1950) who found 180–390 µg %. Investigations of EP in sideropenic anemia has also been made by Watson (1946), his values varying from 50–600 µg %. Cartwright *et al.* (1948) found 100–475 µg %; Ventura *et al.* (1954 b) 46–302 µg % and Pagliardi *et al.* (1959) 178–663 µg %. The observation of Watson (1946) that high EP values were more common in patients with "epithelial" symptoms seems to be supported, but the present material is too small to allow safe conclusions.

Changes of EPP during therapy. During the period of iron treatment, EPP was studied with short intervals. The results are shown in Figure 16–19. The day after the start of iron administration, blood samples were obtained from three patients. When compared to the initial EPP levels, two of the patients' EPP had increased; the other patient's EPP had decreased.

After ten to fourteen days, all patients had considerably lower EPP values than those initially observed. The most pronounced reduction was found in case 1: 215 µg %, corresponding to 42 % of the initial value. In cases 2, 3 and 4, the reduction was 84, 92 and 66 µg % respectively (28, 43 and 25 %). Cf Figure 16–19.

Since ECP was found to be small, comparisons can be made with earlier investigations. In three patients, Pagliardi *et al.* (1959) noticed that EP increased during the days after the start of therapy. In these patients, decrease of EP supervened after 3–10 days, but values below the initial levels were not achieved until the 7th to 22nd day.

In two other patients studied by Pagliardi *et al.*, the rate of EP reduction was even greater than that observed in the present study. One patient's EP decreased from 232 to 72 µg % in 10 days; another patient's EP was reduced from 179 to 82 µg % in 9 days. In the studies of Watson *et al.* (1944) and Cartwright *et al.* (1946) iron was administered orally. In Watson's patient EP decreased from 613 to 427 µg % in eight days. In Cartwright's three patients, EP decrease did not start until 10–20 days after the beginning of the therapy; after this start, the decrease of EP was rapid.

Initial values of ECP. The initial ECP

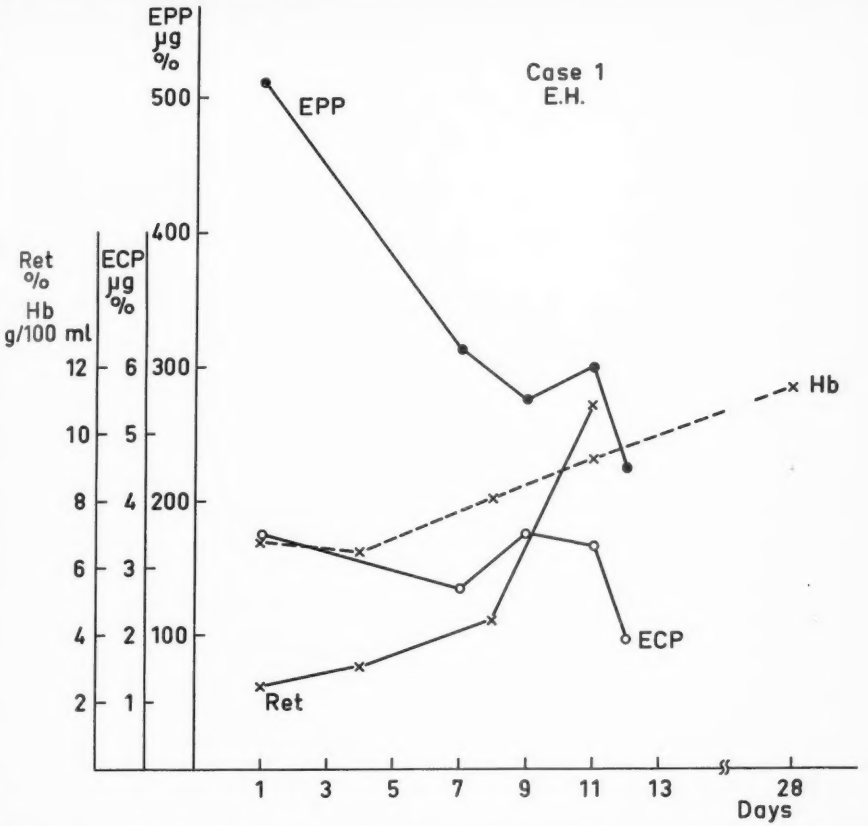

Fig. 16. Changes of free erythrocyte copro- and protoporphyrin in case 1, E.H. From day 1, iron was given intravenously. Hb = hemoglobin concentration. Ret = reticulocyte count.

values ranged from 0.9–3.5 µg %. In case 1, ECP was found to be 3.5 µg % which is higher than the maximum ECP found in normal females, but 2.4 % reticulocytes were also found.

Earlier, the ECP in iron deficiency anemia has been studied by Watson (1950). In four cases, ECP varied between 1.0 and 5.0 µg %. The highest value occurred in a patient with 4.2 % reticulocytes. The present findings confirm Watson's results.

Changes of ECP during therapy. Watson's study (1950) established a close correlation between ECP and the degree of reticulocytosis during the B_{12}-induced remission of pernicious anemia. The present investigation of iron deficiency anemia treated with iron did not reveal any correlation between ECP and reticulocyte count during the course of therapy (Fig. 16–18).

Results of ECP and EPP determinations in normal females. Initial values were within normal limits. After the intravenous

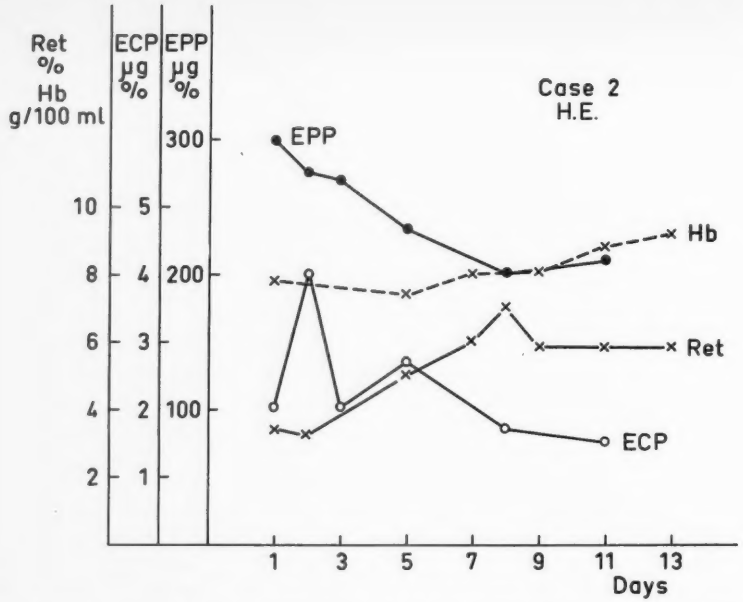

Fig. 17. Changes of free erythrocyte copro- and protoporphyrin in case 2, H.E. From day 1, iron was given intravenously. Hb = hemoglobin concentration. Ret = reticulocyte count.

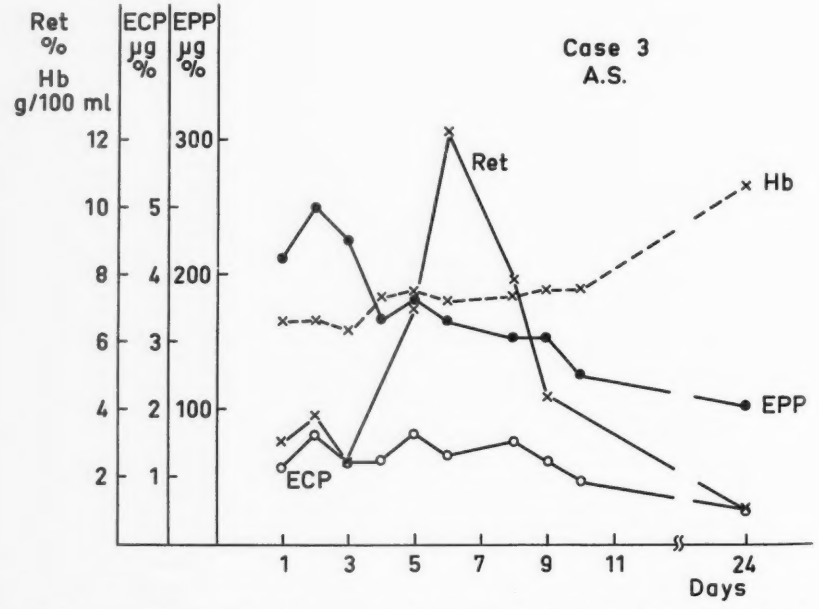

Fig. 18. Changes of free erythrocyte copro- and protoporphyrin in case 3, A.S. From day 1, iron was given intravenously. Hb = hemoglobin concentration. Ret = reticulocyte count.

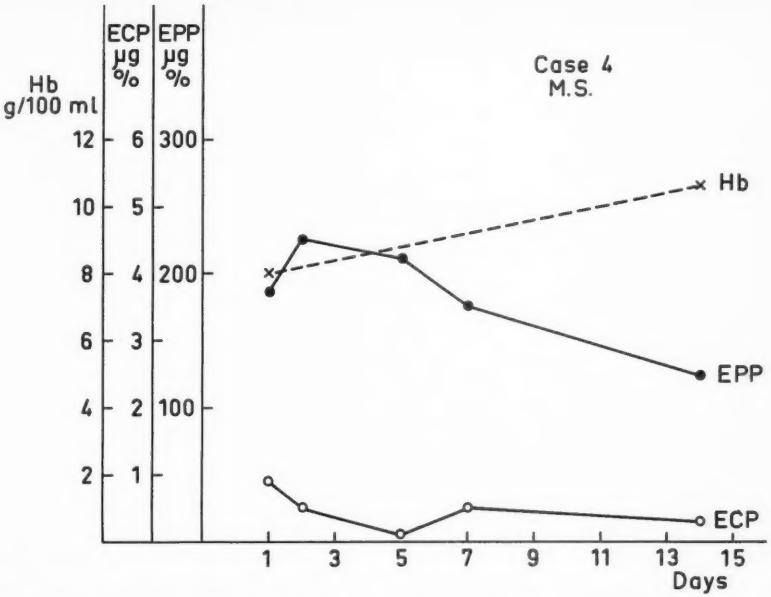

Fig. 19. Changes of free erythrocyte copro- and protoporphyrin in case 4, M.S. From day 1, iron was given intravenously. Hb = hemoglobin concentration.

administration of saccharated iron oxide, a slight decrease of EPP could be observed in one individual (Table 24). Simultaneously, the ECP was diminished in this individual. Hematocrit values remained unchanged.

Patho-physiological aspects

Protoporphyrin. Cartwright *et al.* (1948), discussing the EP of sideropenic anemia, have explained the increased EP in the following manner. In this anemia the

TABLE 24. *Changes of ECP and EPP after iron administration to healthy individuals.*

	Day	Iron given mg	EPP µg %	ECP µg %	Hematocrit %
L.B.	1	40	35.8	0.7	41.5
23 years	2	100	33.6	0.3	41.5
	6	—	27.5	0.1	41.5
	12	—	28.4	0.4	40
G.E.	1	40	40.9	0.5	42
29 years	2	100	40.2	0.5	42
	6	—	37.5	0.8	43
	12	—	39.5	0.4	43

porphyrin synthesis seems to be intact, while iron is not available for the synthesis of hemoglobin. Thus the free protoporphyrin is accumulated, representing an uncompleted hemoglobin synthesis. Since there were indications that reticulocytes contain more free protoporphyrins than mature cells (Watson and Clarke 1937; Grinstein *et al.* 1948), Cartwright *et al.* assumed that the free porphyrin in iron deficiency anemia was to be found chiefly in the reticulocytes. However, it was not explained how the free protoporphyrin disappeared during the maturing of the erythrocyte, whether by incorporation in hemoglobin, by catabolism or by removal from the erythrocytes.

Recent investigations by Goldberg (1959) and by Grinstein, Bannerman and Moore (1959) have established, that reticulocytes have the ability to form heme from iron and protoporphyrin. Mature erythrocytes do not seem to have the enzymes necessary for a noticeable heme synthesis. Thus it is assumed that the free protoporphyrin can disappear from the mature erythrocyte only by catabolism or by removal from the erythrocyte.

In the present study of EPP changes during iron therapy of iron deficiency anemia, it was found that during ten days the concentration of EPP decreased by 25–43 %. Similar and even greater EP-reduction has been found by Pagliardi *et al.* (1959). A catabolism or removal of the protoporphyrin caused by the injection of saccharated iron oxide *per se* seems unlikely, since the changes of EPP in normal controls were small. Assuming that (1) erythrocytes of all ages contain equal amounts of protoporphyrin, (2) the erythrocytes formed after the beginning of the iron therapy have very little protoporphyrin and (3) mature erythrocytes cannot synthesize heme from iron and protoporphyrin, the maximal reduction of EPP can be calculated from estimates of the total erythrocyte volume and of the rate of destruction of old erythrocytes. Using the hematocrit as an index of the changes of the total erythrocyte volume (Mollison 1956) and presuming a 10 % destruction of old erythrocytes after 10–11 days, such calculations have been carried out by the present author. It was found that in case 2 only, the rate of the EPP reduction was consistent with the three assumptions mentioned above. However, the finding of increasing EPP values during the first days following the beginning of iron therapy (cases 3 and 4) indicates that the newly formed erythrocytes contain considerable amounts of free protoporphyrin. If the observations just mentioned (Goldberg 1959 and Grinstein *et al.* 1959), are valid for mature erythrocytes of iron deficiency anemia, the conclusion must be drawn that the free protoporphyrin has not been distributed uniformly in the entire erythrocyte population before the treatment.

On the other hand, the free protoporphyrin is probably not present in the reticulocytes only. Observations failing to establish a relationship between the EPP and the reticulocyte count have been made by Watson (1944, 1946, 1950), and by others, in hemolytic anemia and during the treatment of pernicious anemia. Also, in the present study, no parallelism between the EPP concentration and the reticulocyte count could be found during the treatment.

Although the experimental findings do

not allow definite conclusions, the results suggest that the free protoporphyrin in iron deficiency anemia is present both in the reticulocytes and in the young mature erythrocytes. The mechanism by which the free protoporphyrin may disappear from the ageing erythrocyte is not known.

The immediate EPP-response to intravenous iron therapy was found to vary. In two patients, now studied, as well as in two patients observed by Pagliardi *et al.* (1959), the EPP increased during the first days of iron administration. In another case of the present study, the EPP at once showed a distinct downward trend. Stiefel and Jasiński (1954) have demonstrated that in animals the transition of labelled iron from saccharated iron oxide to the circulating transferrin is very rapid, labelled iron appearing in transferrin within an hour. After the injection of saccharated iron oxide in patients, an immediate transfer of iron to transferrin has been demonstrated by Hagberg (1953b). Thus an immediate decrease of EPP is possible although an increase is more often found. Further investigations are necessary for the explanation of this discrepancy.

The conclusions that can be drawn from the changes of ECP during iron administration to patients with iron deficiency anemia are limited by the uncertainty of ECP determinations in the presence of great concentrations of EPP (Chapter III). However, the present findings indicate that during the iron administration, no parallelism exists between the ECP level and the reticulocyte count. In this respect, the reticulocytes of iron deficiency anemia in remission differ from those of pernicious anemia in remission.

CHAPTER X

General discussion and conclusions

Since the detection of free erythrocyte protoporphyrin in 1928 by van den Bergh and Hyman, a comprehensive literature has accumulated on this subject. At least twenty publications have appeared on the quantitative determination of free protoporphyrin in erythrocytes. The determinations of the protoporphyrin content of normal *whole blood* have given contradictory results; in the study of van den Bergh, Grotepass and Revers (1932), 2–12 μg % were found, while in the study of Lageder (1936) a variation of 10–120 μg % was found.

Later, most authors calculated the protoporphyrin content per 100 ml *erythrocytes*, thereby enabling a comparison between normal and anemic subjects. These values, too, have been most varying. Schumm (1939) found the free erythrocyte protoporphyrin in normal subjects ranging from 11–17 μg %, with the average 13 μg %; while Ward and Mason (1950) found it ranging from 13 to 139 μg %, the mean erythrocyte concentration being 43 μg %. It seems unlikely that these widely scattered results are merely due to variations in the actual porphyrin content. According to the author's experience, a considerable variation in the results is obtained by small differences in the procedure.

Free erythrocyte coproporphyrin, first described by Watson in 1950, probably has been included in most of the earlier determinations of free protoporphyrin, and hence the name free porphyrin is more appropriate. In normal subjects, the concentration of free coproporphyrin is small compared to that of free protoporphyrin. The mean ECP values found in healthy adults range from 0.5 μg % (Watson 1950) to 1.5 μg % (Prato *et al.*, 1959). It seems likely that the variations in these values are due not only to real variations between the materials but also to differences in the analyses. It is, of course, important to remove the plasma from the erythrocytes since a coproporphyrin-like pigment has been found in plasma (Chapter VIII).

In the present investigation, our main attention has been directed to methodological work in order to make the method practical for routine clinical use. The different steps of the analysis have been investigated and a standardized procedure adopted. The influence of hematin on the protoporphyrin determination has been greatly reduced. The effect of co-extracted protoporphyrin on the coproporphyrin determination has been suppressed by a special procedure. Since recovery experiments revealed that losses of porphyrin during the analysis are inevitable, a special correction of the results was introduced.

The present investigation of normal adult males and females showed the mean EPP

to be 30 and 37 μg %, respectively. These findings are consistent with recent results. The mean ECP values found in males of 1.3 μg % and in females of 1.2 μg % are a little higher than those found by other investigators. This is thought to be due to differences in methods and/or correction procedures.

ECP and EPP were studied in cord blood from 20 newborn infants and in venous blood from 41 infants 9 days—19 months old (Chapter VII). At birth, both ECP and EPP were found to be elevated compared to the normal values of adults. The increased ECP in cord blood is assumed to be due to the increased erythropoiesis present at birth and during the last part of the fetal life. This assumption is supported by the finding of normal adult ECP values in full-term infants 9–15 days old. At this age, all signs of increased erythropoiesis generally have disappeared. The findings of increased EPP levels in cord blood are more difficult to explain. As has been concluded earlier (Chapter VII), it would seem probable that the most important factors causing the increased EPP at birth are (1) the hypoxia of the fetus, and (2) the accelerated hemoglobin synthesis. Of course, some special unknown conditions, occurring only in newborn babies, cannot be excluded. During the first four months of life, EPP values have been found to be essentially constant and distinctly increased when compared to normal adults. A perusal of the literature revealed that in other conditions with increased EPP, decreasing EPP values were found within a few weeks or a month after the elimination of the causal factor. Since the low oxygen tension of the fetus is abruptly alleviated by delivery and the accelerated rate of the erythropoiesis is changed into a normal or subnormal rate within the first week of extra-uterine life, the constantly increased EPP found in infants up to four months of age is left unexplained. Among other known factors causing increased EPP, e.g., iron deficiency, anemia of infection, lead poisoning, only iron deficiency could possibly occur in apparently healthy infants. However, iron deficiency is very seldom found before the age of four months.

It thus seems necessary to assume that the infant less than four months old deals with the free protoporphyrin in a manner different from that of the adult. It could be postulated that the infant's bone marrow, although subnormal in activity and adequately supplied with iron, is—for some reason—discharging red cells with an unusually high content of free protoporphyrin. But in that case, it is difficult to explain why the EPP is almost unaffected by the transition from the active erythropoiesis at birth to the depressed one of full-term infants one week to three months of age.

It could also be suggested that some physiological minimum level of EPP exists. This level, then, could be higher in infants than in adults. In fact the earlier and present investigations of normal adults have revealed that EPP (or EP) values seldom are lower than 15–20 μg %. Even in patients with aplastic anemia and biochemical signs of well-filled iron stores and in patients with hemochromatosis, the EPP values are not much lower (Ventura *et al.* 1954 b). Thus a minimum level of EPP seems to occur in adult individuals. A similar phenomenon in very young infants does not appear improbable.

Yet it is difficult to suggest a mechanism by which the varying "minimum EPP level" is caused. One possibility may be that the free protoporphyrin is not a uniform substance. Considering coproporphyrin, at least three different analogues can be expected to occur in the erythrocytes; viz., coproporphyrinogen III, an intermediate of heme synthesis; coproporphyrin III, the oxidized analogue of the former; coproporphyrin I. Only coproporphyrinogen III can be utilized for the synthesis of protoporphyrin and it is probable that this process also takes place in circulating reticulocytes. It may be, therefore, that the coproporphyrinogen III concentration in the reticulocytes decreases while that of coproporphyrin I and III remains unchanged. Thus a "minimum ECP level", caused mainly by the two latter porphyrins could be explained.

Protoporphyrin IX, on the other hand, is the precursor of heme (Heikel, Lockwood and Rimington 1958). The reduced analogue, protoporphyrinogen, is probably easily autoxidized. No isomers other then type IX have been found. Thus for protoporphyrin, a "minimum EPP level" cannot be explained in this manner.

Studies of iron deficiency anemia have been described in Chapter IX. It was concluded that the increased EPP was situated chiefly in reticulocytes and young mature erythrocytes in these patients. Thus a process must be assumed by which the EPP content is reduced during the ageing of the erythrocytes. The rate of this reduction can be expected to influence the minimum EPP level. If this rate is slower in the very young infant than in the adult, an increased minimum level of EPP would follow.

The present investigation was undertaken to study the physiological behaviour of free copro- and protoporphyrin during infancy. Characteristic changes of the free porphyrins in disease have been noted by earlier investigators in, among others, the anemias of hemolysis, iron deficiency and infection. Furthermore, a disturbance of the porphyrin metabolism with altered levels of free porphyrins has been found not only in such diseases as erythropoietic porphyria but also in a certain type of hypochromic anemia (Garby, Sjölin and Vahlquist 1957). Additional cases have been reported recently. Determinations of free erythrocyte copro- and protoporphyrin can, therefore, contribute to the diagnosis of cases of atypical hypochromic anemia.

Summary

Methodological Studies

A method for the simultaneous determination of free erythrocyte copro- and protoporphyrin is described. Coproporphyrin is determined fluorometrically after a final extraction with 0.24 *N* HCl, while protoporphyrin is determined spectrophotometrically after a final extraction with 5 *N* HCl. The details of the analysis have been investigated and recovery experiments performed. Since losses of porphyrins always occurred, suitable corrective equations were used.

The nature of the extracted porphyrins was checked. Protoporphyrin was identified in the 5 *N* HCl extracts. In the 0. 24 *N* HCl extracts, the identity of coproporphyrin could be experimentally corroborated.

Clinical Studies

In healthy male adults, the mean concentration of free erythrocyte protoporphyrin was found to be 30 μg % and that of coproporphyrin 1.3 μg %. The corresponding mean values in females were 37 μg % and 1.2 μg %.

Divergent values were found in early infancy. In cord blood, the content of free protoporphyrin was 54 μg % and that of coproporphyrin 2.8 μg %. During the first week of life, the latter concentration decreased rapidly; in infants 1–2 weeks old, the mean concentration was down to 0.9 μg %. The free protoporphyrin remained nearly unchanged during the first four months of life. After that, fluctuating values supervened. Beginning about the age of one year, the values approached those for normal adults.

The free protoporphyrin has also been studied in erythrocytes from iron deficiency patients before and during iron therapy. The protoporphyrin concentration decreased considerably during treatment.

In plasma, a coproporphyrin-like pigment has been found. The mean concentration in adult plasma corresponded to 0.8 μg coproporphyrin per 100 ml. In cord blood plasma, the concentration corresponded to 1.5 μg per 100 ml.

The findings are discussed and put in relation with other known physiological processes during infancy. The conclusion is drawn that erythrocytes of the very young infant deal with the free protoporphyrin in a dissimilar manner from that of the adult's erythrocytes.

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